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LIVER FUNCTION IN HEPATITIS *

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THE effective morbidity incidence of hepatitis during the war was very great, due not only to the large number of individuals affected but also to the long period of disability. Considerable evidence has been obtained that complete bed rest early in the course of the disease is likely to result in a shorter and milder illness with fewer residual abnormalities.[1, 2, 3] It has also been reasonably well established that to return to physical activity before adequate subsidence of the disease is to invite a relapse which may be more severe than the initial attack.[1, 3] One of the main problems, therefore, was to detect the disease in its incipient stage and to be able to recognize when it was reasonably safe for the individual to resume normal activity with a minimal danger of relapse. The considerable incidence of hepatitis without tangible jaundice [3] has, of course, constituted a very important facet of this whole problem. In addition, the differential diagnosis of jaundice, especially in cases of sporadic type, has emphasized the need of a thorough study of liver function. It has become increasingly evident that such a study must be of composite type if one is to expect any considerable degree of accuracy, either in the differential diagnosis of jaundice or in the detection of latent or residual hepatic injury. Single tests are likely to prove misleading because of remarkable variation from case to case. Examples of this will be discussed subsequently.

The discussion which follows is based upon the clinical and laboratory study of 70 cases of hepatitis, including 21 cases of chronic hepatitis with varying degrees of hepatic cirrhosis. Some of these have been considered in detail elsewhere.[4] The discussion is also based in part upon observations by one of us (C. J. W.†) on many cases of hepatitis in various Army Hospitals, especially the Schick General Hospital at Clinton, Iowa.

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In considering liver functional disturbances, whether in hepatitis or in any other hepatic disease, it is helpful to keep in mind the three functioning units of the liver, namely (1) hepatocellular, (2) cholangiolar, (3) reticuloendothelial. The available laboratory procedures permit one to gain information about the function of the first two only. While there can be no doubt that the Kupffer cells are often seriously affected in hepatitis, there is at present no means by which one may assay their function or determine the degree of injury which they may have sustained.

The term "cholangiolar" refers especially to what has also been spoken of as the intermediary portion [8] of the intrahepatic biliary tract including the ampullae of the bile capillaries at the periphery of the liver lobule, as shown in figure 1 which has been redrawn from an illustration in Eppinger's

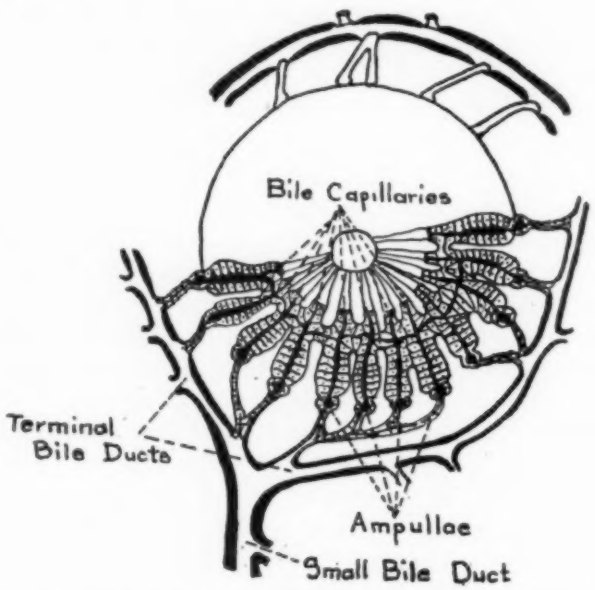

FIG. 1. Schematic drawing of the intrahepatic bile duct system. Redrawn from Eppinger.[5] The term cholangiole, as used in the text, refers to the ampullae of the bile capillaries, the terminal bile ducts, and their connections.

"Diseases of the Liver".[5] There is considerable evidence that these ampullae are especially vulnerable to injury or increased pressure, in fact, Aschoff has referred to them as the "Achilles heel of the biliary tract." [6] The functions listed in table 1 are believed to relate especially to hepatocellular or cholangiolar function as indicated.

It is seen in table 1 that an increase of the delayed, or indirect reacting serum bilirubin is related to hepatocellular functional disturbances, while an increase of the 1′ or prompt reacting type is thought to be an evidence of cholangiolar abnormality. This, together with some of the other items listed in table 1, will be discussed in more detail in the following.

TABLE I

Evidence of Hepatocellular and Cholangiolar Functional Derangement Due to Diffuse Liver Disease

1. Hepatocellular:

   Increased delayed reacting bilirubin
   Increased urobilinogen in urine
   Diminished galactose clearance
   Diminished hippuric acid synthesis
   Diminished serum albumin
   Diminished cholesterol ester fraction
   Positive Hanger test (cephalin-cholesterol flocculation)
   Positive Maclagen test (thymol turbidity)? (vide infra)

2. Cholangiolar:

   Increased prompt reacting (1′) bilirubin
   Bilirubinuria
   Bile salts in blood and urine
   Increased total cholesterol in blood
   Increased serum alkaline phosphatase

Patients with hepatitis are seen in whom the evidence of liver functional derangement is mainly hepatocellular and again, mainly cholangiolar. In many cases, various mixtures of the two are observed. The results of the present study, as well as of others conducted in recent years,[2] indicate that these variations are largely a matter of stage of the disease and that it is not possible to separate an hepatocellular form as a disease entity distinct from a cholangiolitic form, as has been suggested by Eppinger[5] and others.[8] It is nevertheless evident that the late stage of the disease is in some cases of a relatively pure cholangiolitic type, characterized mainly in other words by the evidences of cholangiolar functional disturbance. Closely correlated with these, especially the last three listed in table 1 is the presence of pruritus. Such cases, particularly if sporadic, offer real difficulty in diagnosis since they closely simulate extrahepatic biliary obstruction.

In studying liver function under any circumstances, and especially in a disease such as hepatitis in which serial observations, often on a large scale, are essential, it is clear that simple tests related to natural substances are preferable to more complex procedures especially those demanding administration of a given material and subsequent quantitative determination in blood or urine. This assumes, of course, that the simple procedures are of equal or greater value than the more complex ones which is not always the case, particularly if the stage of the disease be taken into account. Thus, the experience gained in the last two years, as exemplified in the report of Gellis and Stokes',[9] indicates that the simple procedure for bilirubin in the urine is probably fully as useful as the bromsulfalein test in the early stage of the disease. In the late defervescent period, on the contrary, the value of the two tests is quite reversed. This will be referred to again. The tests for bilirubin and urobilinogen in the urine are the only procedures which lend themselves readily to everyday bedside diagnosis. It was quite unfortunate, therefore, that when epidemic jaundice began to be a major

problem some five years ago, the great usefulness of these simple tests was often ignored or overlooked.

This may be ascribed to two causes: The neglect of the urine bilirubin test may be attributed to the generally accepted concept [5, 10] that bilirubin does not appear in the urine until the serum bilirubin has become elevated to 2 mg. per 100 c.c., a level in other words at which jaundice is usually manifest. As will be pointed out in more detail a little later, this concept has had to be abandoned. The cause of the rather general failure to utilize the Ehrlich reaction for urobilinogen in the urine appears to have been the relative insensitivity and frequently misleading results of the dilution technic of estimation such as that described by Wallace and Diamond.[11] This method, to be interpreted as positive, requires a color reaction with a dilution of 1:20, a dilution which excludes many instances in which there is a significant increase in urobilinogen excretion, especially if the urine be relatively dilute to begin with.

In discussing our experience with individual procedures used in the study of hepatitis, the serum and urine bilirubin will be considered first.

Neefe and his associates,[7] while studying infectious hepatitis which had been induced in human volunteers, observed that bilirubin often appeared in the urine at the onset of the disease *before* the total serum bilirubin had exceeded 1 mg. As already noted, this was contrary to general belief but it does appear that George Budd had recognized the same phenomenon as early as 1846.[12]

"The coloring matter of bile may be detected in the urine even before the skin becomes yellow and in some cases the readiness with which it passes off in the urine seems to prevent the occurrence of jaundice—the skin retaining its natural color while the tint of the urine attests to the presence of bile."

Although Budd did not estimate the serum bilirubin level, it seems highly probable that he was the first to describe hepatitis without jaundice, as well as the bilirubinuria in the preicteric stage of hepatitis with jaundice. In retrospect, it is really not too astonishing to find a lack of correlation of the presence or absence of bilirubinuria with the level of total serum bilirubin. It has long been known that in pure retention jaundice, as for example, hemolytic jaundice, in which the van den Bergh reaction is delayed or indirect, the total serum bilirubin may be considerably higher than 2 mg. and yet bilirubin is not found in the urine. Using the qualitative method only, van den Bergh [13] recognized long ago that the prompt reaction, which is associated with bilirubinuria, is usually complete within one minute, the delayed reaction taking place thereafter. This is better appreciated if one simply plots a direct van den Bergh reaction against time (figure 2), the prompt component being represented by a steep rise within the first minute, after which there is a rather abrupt shoulder and a slow continuous increase over a longer period.[14, 15, 16] If one adds alcohol at any point along this

latter part of the curve, one simply induces the remainder of the bilirubin to combine much more quickly with the diazo compound, bringing out what is known as the indirect reaction. If this had been done at 8 minutes, for example, the curve would have risen sharply again at that time. The delayed and indirect reacting bilirubins are believed to be identical. The available evidence suggests that this type is still attached to the globin derived from the hemoglobin molecule, while the prompt reacting type is probably sodium bilirubinate as formed in the bile.[17] Some investigators have believed that there is but one type of bilirubin, the difference between prompt and delayed reactions depending simply on time and amount. If this were true, however,

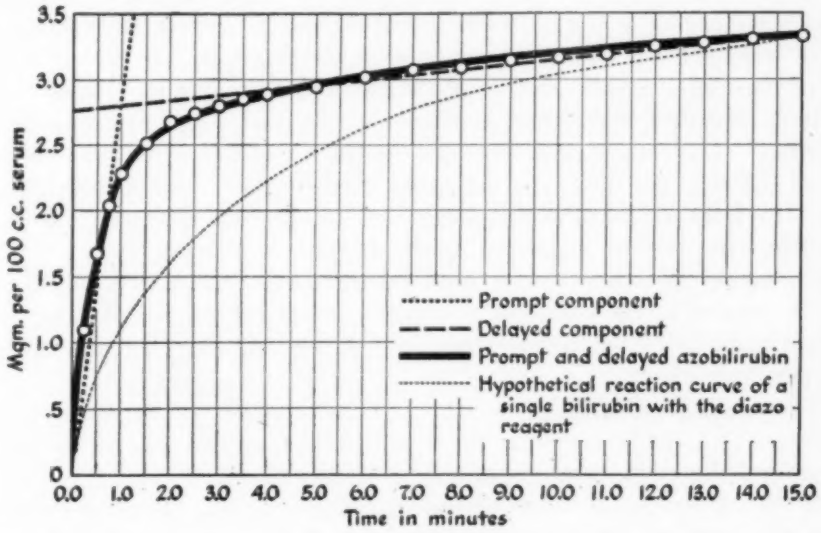

FIG. 2. Reaction curve of prompt and delayed direct reacting serum bilirubin compared with hypothetical (parabolic) curve of a single bilirubin with diazo reagent: (From article by C. J. Watson: Some newer concepts of the natural derivatives of hemoglobin, Blood, Jr. of Hemat., 1946, i, 99.) Reproduced by permission of the publishers, Grune and Stratton, Inc., New York, N. Y.

one would expect a parabolic reaction curve, such as shown by the dotted line (figure 2) rather than that actually found, and which clearly reveals the presence of two distinct types.

There is much reason to believe that the prompt or one minute bilirubin, as represented by the more vertical component, is that which is related to the appearance of bilirubin in the urine.

Using the fundamental classification of jaundice as proposed by Rich,[18] regurgitation jaundice is characterized by an increase of prompt reacting bilirubin in the serum, together with bilirubinuria. In retention jaundice the delayed reacting bilirubin is increased and bilirubin is absent in the urine. The existing evidence indicates that regurgitation may occur because of increased intrabiliary pressure, with rupture of cholangioles, or toxic chol-

angiolar injury with increased permeability.[5, 6] This has been discussed in more detail in a recent communication.[16] As already noted, there is considerable reason to believe that the ampullae of the bile capillaries are most vulnerable in this regard, but the question must remain open for the time being as to whether there is regurgitation from the bile capillaries or whether the bilirubinglobin of the blood is converted to the prompt reacting bilirubin by the Kupffer cells and passed at once into the lymph, thence into the thoracic duct and thus into the blood. Recent studies by Gonzalez-Oddone,[21] in this laboratory, on experimental regurgitation jaundice in dogs, have shown that the prompt reacting bilirubin, along with other elements of the bile, gains access to the blood, at least in considerable measure, via the lymph. In these experiments, the bilirubin appearing in the thoracic duct lymph was almost wholly of the one minute or prompt reacting type.

Surprisingly enough, the range of values for the one minute or prompt reacting bilirubin in normal individuals has not been determined until recently.[16] Our experience thus far, at least, indicates that this does not exceed 0.2 mg. per 100 c.c., the great majority of values being less than 0.1. It is believed that the 1′ and the total are the only values of importance, the difference, or T–1′ representing the delayed or indirect type.

The study of cases of infectious hepatitis has shown that bilirubinuria may be present at the outset of the disease when but minor elevation of the prompt reacting bilirubin has occurred. A striking example was described in a previous report.[16]

The finding of bilirubin in the pre-icteric stage of hepatitis is quite in accord with the history that these patients commonly give of "dark urine for several days before the appearance of jaundice."

In the defervescent stage of the disease, however, bilirubin disappears from the urine at relatively high levels of the prompt reacting bilirubin, usually between 0.8 to 1.2, at times even higher.[16] In one case which we have studied, there was no bilirubinuria even though the prompt reacting serum bilirubin was 3.0 mg. It is evident that the renal threshold in the early or pre-icteric stage, is lower that it is during defervescence.

The importance of early bilirubinuria in diagnosis, especially in the pre-icteric stage of hepatitis, clearly indicated the need of a simple and reliable method which could be applied to mass and serial usage.

At the suggestion of Dr. Roy H. Turner, the "barium or filter strip" modification of Harrison's test for bilirubin in the urine was devised.[23, 24] It consists simply in impregnating strips of a specially retentive thick filter paper with barium chloride. These strips are then inserted into the urine sample to be tested, held perpendicularly for a moment or two during which the urine runs up by capillary attraction and the pigments collect at the surface of the urine. Fouchet's reagent is then dropped upon this surface zone with the result that if bilirubin is present, a green color is noted. The test is sensitive to as little as .05 mg. per 100 c.c. of urine, although in many

samples concentrations less than 0.1 mg. per 100 c.c. are doubtful. The method has been adapted to a semiquantitative colorimetric procedure.[24] The ease of application is obvious and it is believed that this test could be added with much advantage to the routine urinalysis. It may be regarded as one of the two tests of liver function which lend themselves to bedside diagnosis. The other is the urine Ehrlich reaction for urobilinogen.

It might be pertinent at this time to review very briefly the present concept of the origin and fate of urobilinogen (figure 3). As already noted, it

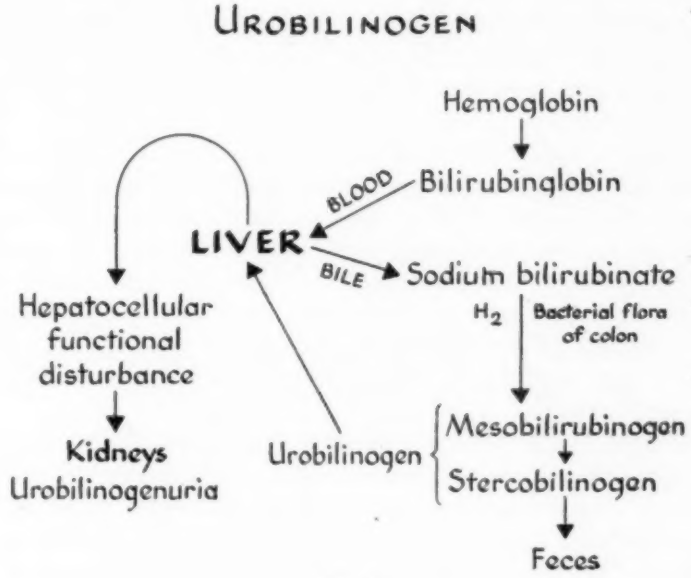

FIG. 3.

is believed that bilirubinglobin is changed in the liver to sodium bilirubinate and from this the urobilinogen is formed by the reducing action of the bacterial flora of the colon. Actually, two very similar colorless chromogens result, both of which fortunately give an Ehrlich reaction of equal intensity.[25, 26] The term "urobilinogen" refers to the composite of these two chromogens. As indicated in figure 3, a considerable fraction of the urobilinogen thus formed is reabsorbed from the colon into the portal circulation and returns to the liver, through which, if there is hepatocellular functional disturbance of any appreciable degree, the urobilinogen goes into the general circulation and is excreted by the kidneys. There are several "if's" in this sequence that must be taken into account in clinical diagnosis. Thus, if little or no bile reaches the intestine, urobilinogen will be found in a very small amount, or not at all, and even though the liver is injured, urobilinogen may not be found in the urine.[27] This state of affairs characterizes many cases of hepatitis during the most severe phase of the disease, when jaundice is at its peak and little or no bile is entering the intestine. If the intestinal

contents move through the colon so rapidly that there is little time for reduction or reabsorption, as for example, with marked diarrhea, there may not be urobilinogenuria even though liver damage exists. If there is enough renal insufficiency to cause nitrogen retention, urobilinogen may also be retained.[28, 29]

The qualitative Ehrlich reaction or test for urobilinogen in the urine is very simple.[29] It is particularly useful when applied serially by the same individual. It is recorded simply as a trace, indicated by a faint pink, on up to 4 plus, which is an intense red-blue color. The use of sodium acetate, as first recommended by Terwen,[30] is very important in this reaction.[31] In the first place it greatly intensifies the color, and in the second it largely or completely abolishes any color due to indole or skatole, which also react with the aldehyde.

In our experience, 95 per cent of normal individuals excrete less than one Ehrlich unit per 2 hour sample, while about 5 per cent excrete between 1 and 1.5 units.[32a] There is little doubt that the method is much more reliable if used serially, as the excretion of urobilinogen fluctuates from day to day and at various times within the same day. For this reason it must be emphasized that in some cases of liver disease the single or 2 hour sample may be normal, yet the 24 hour urine urobilinogen [31] may be considerably increased.[32b] Unfortunately, the latter determination does not lend itself well to mass or serial usage.

Hallock and Head [33] have used the semi-quantitative urine Ehrlich method in studying a group of cases of hepatitis seen during the first few days of the disease. Twenty of these subsequently developed jaundice, of which number 18 exhibited significantly positive Ehrlich reactions during the preicteric stage. They also studied 78 individuals in the same epidemic who did not develop jaundice subsequently, and who were classified as cases of hepatitis without jaundice although it was known * that quite a number of this group had dark urine and slightly elevated icterus indices. In this group 88 per cent had positive reactions, as compared with 5 per cent in the control series.

Table 2 includes the data from one of Hallock and Head's cases showing the early appearance of urobilinogen with a normal icterus index, the fluctuation in amount from day to day, the disappearance at the height of the jaundice, and then the return during the early defervescent stage. It may be emphasized that this return of urobilinogen in the urine, in other words, the change from a negative to a positive Ehrlich reaction, often heralds beginning improvement. It may be noted that they compared the simple qualitative and the semiquantitative methods, their results indicating that in the hands of the same individual the former method is very helpful. Table 3 includes data from one of Hallock and Head's cases of hepatitis without jaundice. This shows the outspoken urobilinogenuria at the outset of the disease and the rapid disappearance as the patient improved. Our own experience with

* Personal communication.

TABLE II*

Urine Ehrlich Reaction in Epidemic Hepatitis, Pre-Icteric and Icteric Stages

	4 p.m.		9 p.m.		Ceph. Floc. Reaction 24 hr.	I.I.	Hepatic	
	Qual.	Quant. Ehrlich Units/100 c.c.**	Qual.	Quant. Ehrlich Units/100 c.c.**			En.	Tend.
Nov. 22	3+	3.2	0		0	6	1	++
Nov. 23	Trace	0.6	Trace	0.6				
Nov. 24	1+	1.2	0					
Nov. 25	2+	2.4	2+	2.4			1	++
Nov. 26	4+	4.0	4+	4.8				
Nov. 29	4+	8.6	0		3+	33		
Dec. 1	2+	2.4	1+	1.2				
Dec. 3	Trace	0.6	0		3+			
Dec. 5	0		0			74	1	++
Dec. 6	0		0					
Dec. 7	1+	1.2	0				1	++
Dec. 9	2+	2.0					1	++
Dec. 11	4+	8.0			2+	36	1	++
Dec. 13	4+	8.0						
Dec. 18	4+	5.0						
Dec. 23	1+	1.6			1+	16		
Dec. 26	0	0					0	0
Dec. 29	0	0					0	0

I.I.—Icteric index.
En.—Hepatic enlargement in terms of fingers'-breadth below costal margin.
Tend.—Hepatic tenderness in terms of 1 to 3 plus.
* From the Bulletin of the U. S. Army Medical Department, 1946, v, 240. Reproduced by permission of the Surgeon General, War Department, Washington, D. C.
** In the original this was given, incorrectly, as mg. of urobilinogen per 100 c.c.

TABLE III*

Urine Ehrlich Reaction in a Case of Epidemic Hepatitis without Jaundice

	4 p.m.		9 p.m.		Ceph. Floc. Reaction 24 hr.	I.I.	Hepatic	
	Qual.	Quant. Ehrlich Units/100 c.c.**	Qual.	Quant. Ehrlich Units/100 c.c.**			En.	Tend.
Nov. 16	4+	6.0	2+	2.4	0	9	1	++
Nov. 17	3+	4.0	1+	1.6			1	++
Nov. 18	3+	4.0	1+	1.6	0		1	++
Nov. 19	Trace	0.60	0				1	++
Nov. 20	Heavy Trace	0.80	0		0			
Nov. 21	0		0			11	1	++
Nov. 22	0		0		0			
Nov. 23	0		0				0	+
Nov. 24	0		0			8	0	0
Nov. 25	0		0		0			
Nov. 26	0		0					
Nov. 27	0		0			9	0	0

Key of abbreviations as given under table 2.
* From the Bulletin of the U. S. Army Medical Department, 1946, v, 239. Reproduced by permission of the Surgeon General, War Department, Washington, D. C.
** In the original this was given incorrectly, as mg. of urobilinogen per 100 c.c.

the urine Ehrlich reaction in hepatitis indicates that the patient should not be allowed to resume activity until it has returned to and remained at a normal level for several days. Other factors, including of course laboratory data such as is discussed below, must also be taken into account in determining when it is reasonably safe for resumption of activity. As noted at the outset it is believed that any one test of liver function should not be relied upon too strongly, and that composite studies or "profiles" of liver function are more likely to reveal the truth about the presence or absence of liver injury or disease, and at the same time to give some insight into its type and extent. In previous reports [29, 4a, 4b] we have described the use of a single chart to depict a composite study, or "profile" of liver function. While this has proved very helpful and instructive, we have sought to improve the method, and for some time now, have been studying the usefulness of three liver function schedules to facilitate the recording of composite studies. These are printed on small squares of gummed paper which may then be attached to sheets of chart size for incorporation in the patient's record. These schedules have proved very helpful, not only in screening patients for evidence of liver disease, but also in differential diagnosis, and in following the progress of the disease in any given case. The profiles obtained by charting the data in this way, are often indicative of a certain type of jaundice or liver disease.

Schedule No. 1 (figure 4) is used in non-jaundiced cases. It includes, from left to right, the 1 minute or prompt reacting serum bilirubin, and the delayed or total minus 1 minute fraction; this permits ready comparison of the degree of retention and regurgitation factors. The thymol turbidity, indicated by T units, is in the next column; this is a procedure described recently by Maclagan [34] which is probably based on an increase of a certain type of globulin or globulin-lipid complex.[35] The cephalin cholesterol flocculation test (C.C.) of Hanger is included at the top of this column, the result being inserted in terms of a trace to 4 +. Schedule No. 1 also includes the bromsulfalein retention in per cent, 45 minutes after the administration of 5 mg. of dye per kilogram of body weight. As noted there are two columns for the urine Ehrlich reaction in units, on successive days, and one for the urine urobilinogen in mg. for a 24 hour period. The latter, however, need not be done if one or both of the urine Ehrlich tests are significantly elevated. The last column is for the urine coproporphyrin in γ per 24 hours. Lack of this determination need not exclude use of the schedule, although, as noted subsequently, it may often provide valuable information. The "barium strip" modification of the Harrison test for bilirubinuria, as indicated by H, is recorded with the prompt reacting bilirubin, with which, as we have already seen, it is correlated. The horizontal line between the N's represents the upper limit of normal. Values above this line are indicative of liver functional impairment, although it should be emphasized that such elevations, especially when considered singly, may

relate to diseases other than those originating intrinsically in the liver. For example one might find a slight but distinct elevation of the prompt reacting serum bilirubin in a case of common duct calculus without visible jaundice, or one might see a similar elevation of the delayed reacting bilirubin in such conditions as pernicious anemia, hemolytic anemia, or constitutional hepatic dysfunction.

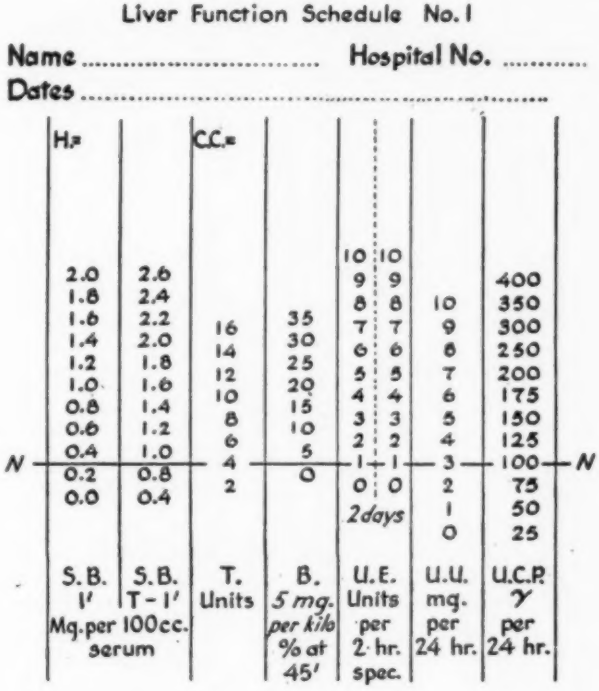

FIG. 4.

S. B. 1' = One minute or prompt reacting serum bilirubin.
S. B. T–1' = Delayed direct and indirect reacting serum bilirubin (T = total).
H. = Bilirubin in urine (barium strip modification of Harrison's test).
CC = Cephalin-cholesterol flocculation test (24 hour reading).
T = Thymol turbidity test (30' reading).
B = Bromsulfalein retention 45' after 5 mg. per kilo. body wt.
U. E. = Urobilinogen in urine (Ehrlich units).
U. U. = Urobilinogen in urine (milligrams).
U. C. P. = Coproporphyrin in urine (gamma).

Liver function Schedule 2 (figure 5) is of particular utility for the jaundiced patient. This schedule is used in differential diagnosis of jaundice and in following the jaundiced patient with respect to progress of the disease. It may also be employed to render the study of any obscure case more complete. It differs from Schedule No. 1 in omitting the bromsulfalein, experience having shown that this test has little or no practical value in the presence of appreciable jaundice. In addition, Schedule No. 2 includes the feces Ehrlich determination which gives an insight into the degree of biliary

obstruction or exclusion of bile from the intestine. This is, however, unnecessary if the urine Ehrlich reaction is significantly increased.

It is seen that a column for the 24 hour urine urobilinogen has been omitted. This determination is regularly carried out, however, in those instances in which the two urine Ehrlich values are negative or border line, and where the diagnosis is still in doubt. In some instances, too, the simple

Liver Function Schedule No. 2

Name ..... Hospital No. .....

Dates .....

	S.B. 1′	S.B. T–1′	F.E.	U.E.		CC	T	C	C.E.	P.
	20.0	20.0				C.C.=			%=	
	18.0	18.0								
	16.0	16.0								
	14.0	14.0	0							
	12.0	12.0	1							
	10.0	10.0	2	10	10					
	8.0	8.0	3	9	9					
	6.0	6.0	4	8	8			25		
	4.0	4.0	5	7	7	16		50	0	
	2.0	2.0	10	6	6	14		75	20	
	1.5	1.8	20	5	5	12		100	45	
	1.0	1.6	30	4	4	10		125	65	
	0.8	1.4	40	3	3	8		150	85	
	0.6	1.2	50	2	2	6		175	105	
N	0.4	1.0	75	1	1	4		200	125	4 N
	0.2	0.8	100	0	0	2		250	150	8
				2 days				300	175	12
								400	200	20
								500		30
										40
	Mg. per 100 cc. serum		Units per 100 Gm.	Units per 2 hr. spec.			Units	Mg. per 100 cc. serum		P. Alk.

FIG. 5.

S. B. 1′ = One minute or prompt reacting serum bilirubin.
S. B. T–1′ = Delayed direct and indirect reacting serum bilirubin (T = total).
F. E. = Urobilinogen in feces (Ehrlich units).
U. E. = Urobilinogen in urine (Ehrlich units).
CC = Cephalin-cholesterol flocculation test (24 hour reading).
T = Thymol turbidity test (30′ reading).
C = Total serum cholesterol.
C. E. = Cholesterol ester content of serum.
P = Phosphatase, alkaline, in Bodansky units per 100 c.c. serum.

quantitative Ehrlich reaction is interfered with by the large amounts of bilirubin present in the urine, and in these it is best to determine the 24 hour urine urobilinogen value.[32b]

The total urinary coproporphyrin determination has also been omitted as experience has shown that it is of little differential diagnostic value in the presence of regurgitation jaundice, whether due to liver injury or extrahepatic biliary obstruction. This study will be discussed in detail elsewhere.

Schedule No. 2 further includes the cholesterol and cholesterol esters and the alkaline phosphatase determination. The total cholesterol is elevated in many cases of obstructive jaundice and in certain cases of paren-

chymal jaundice although it is usually normal or reduced in severe hepatic disease. Since a reduction is more likely to indicate diminishing hepatocellular function, the direction of increase has been placed below the line and the decrease above. The cholesterol esters are characteristically diminished when there is hepatocellular functional derangement. This method has value, however, only if a reliable procedure for determination of cholesterol esters is used, such as the Sperry-Schoenheimer technic.[36] Furthermore, it may be emphasized that the percentage of esterified cholesterol may diminish markedly in the presence of high grade, extra-hepatic biliary obstruction of long standing, hence the value of this finding in differential diagnosis is limited. Marked elevation of alkaline phosphatase occurs when cholangiolar function is disturbed and hepatocellular function is relatively normal, as for example, in the cholangiolitic type of hepatitis and cirrhosis, examples of which will be mentioned. With diminishing hepatocellular function, as in the more severe liver injuries, the alkaline phosphatase is commonly normal or not more than slightly increased. Gutman and his co-workers[37] found that in parenchymal jaundice the alkaline phosphatase is usually less than 10 Bodansky units, while in jaundice due to extrahepatic biliary obstruction it is

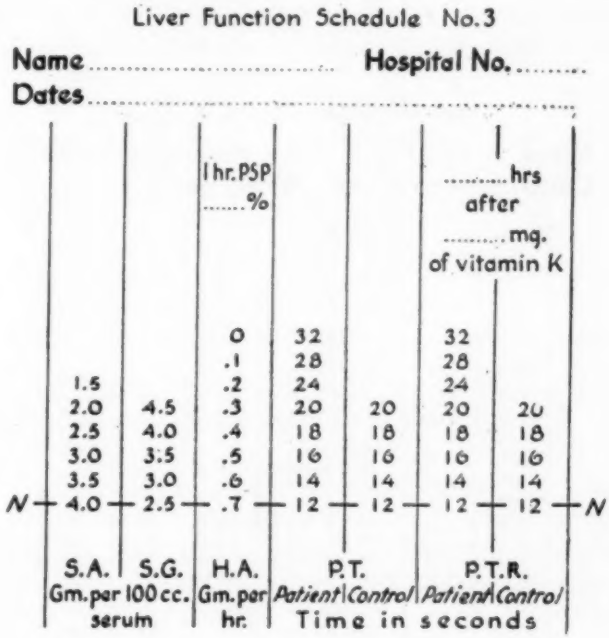

FIG. 6.

S. A. = Serum albumin.
S. G. = Serum globulin.
H. A. = Hippuric acid in urine, one hour after intravenous injection of 1.77 gm. of sodium benzoate (p.s.p. test performed simultaneously).
P. T. = Prothrombin time (Quick's method).
P. T. R. = Prothrombin time response (after vitamin K therapy).

usually well above this level. Because of this we have made the direction of diminution upward in Schedule No. 2, with 4.0 Bodansky units as the upper limit of normal.

Liver function Schedule No. 3 (figure 6) is a supplementary schedule which, so far as the hepatitis problem is concerned, need be used only in exceptional instances. This schedule is of value for differential diagnosis in obscure cases, especially in the presence of ascites, and also in following the progress of the disease in certain instances. It will be noted that the schedule includes, in addition to the fractional serum proteins, the intravenous hippuric acid test, the prothrombin time, and the prothrombin response to vitamin K in those instances in which the initial prothrombin time is abnormal.

Some specific examples of the variations of liver function in hepatitis may now be presented and discussed. Seven cases have been selected because of various points which they emphasize.

The first case is one of epidemic hepatitis in a boy of 14 (L. T.) without jaundice but with dark urine for several days at the outset of the illness, the early period being further characterized by anorexia, nausea and vomiting. The liver was easily palpable and tender. The mother and two brothers also had the disease, the mother being jaundiced. The first composite liver function study is shown in figure 7a. As noted the serum bilirubin, espe-

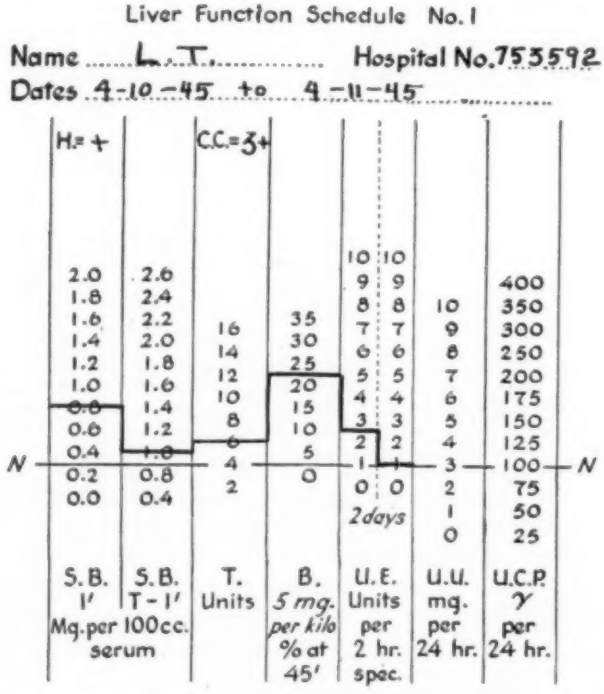

FIG. 7a. *Case 1.* Laboratory studies at time of admission.

cially the prompt reacting component, was distinctly elevated in spite of the lack of visible jaundice. The barium strip test revealed bilirubin in the urine. The other evidences of hepatic functional derangement are shown. A variation in the urine Ehrlich reaction from day to day may be seen. The patient recovered quickly and a week later the liver function study revealed marked improvement, the only residual abnormality being a slightly positive Hanger test and thymol turbidity (figure 7b).

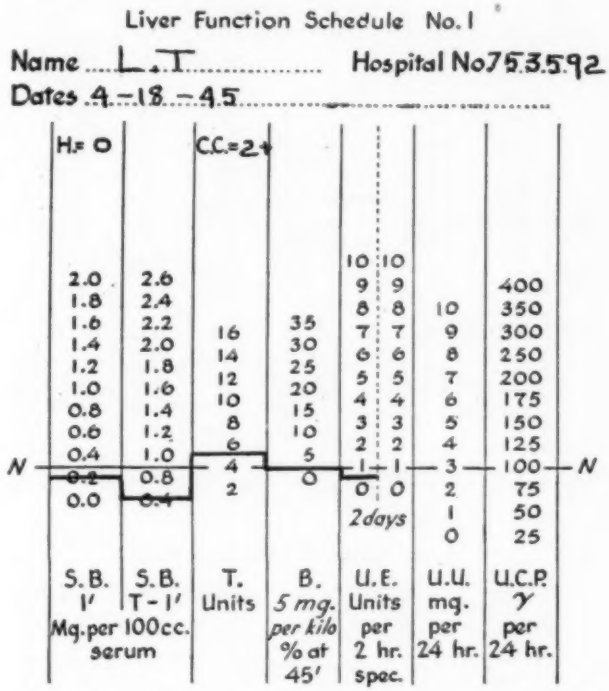

FIG. 7b. *Case 1.* Laboratory studies after one week's hospitalization.

Figure 8a shows the liver function profile from a brother of the preceding case (Case 2, D.T. ♂, 16). This individual had the same sort of an attack at about the same time, also without jaundice but with the abnormal findings as shown. He appeared to recover but, contrary to advice, resumed activity, including the use of alcohol, too soon, and developed a severe relapse, this time with outspoken jaundice, together with marked evidence of hepatocellular functional derangement consisting of high urobilinogen in the urine, markedly positive thymol turbidity, slightly elevated total cholesterol, but low cholesterol esters and relatively low phosphatase (figure 8b). After a prolonged period of bed rest, this patient apparently recovered. A third (partial) composite study was carried out 10½ months later. This is shown in figure 8c.

The third case (K.W. ♂, 32) is that of a severe prolonged epidemic hepatitis with marked jaundice. The composite study in this instance

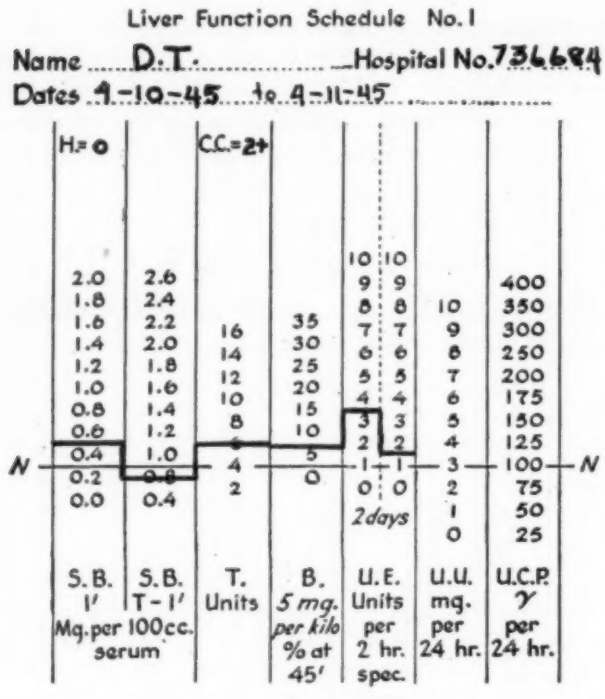

FIG. 8a. *Case 2.* Laboratory studies at time of first admission. Evidence of hepatitis without jaundice.

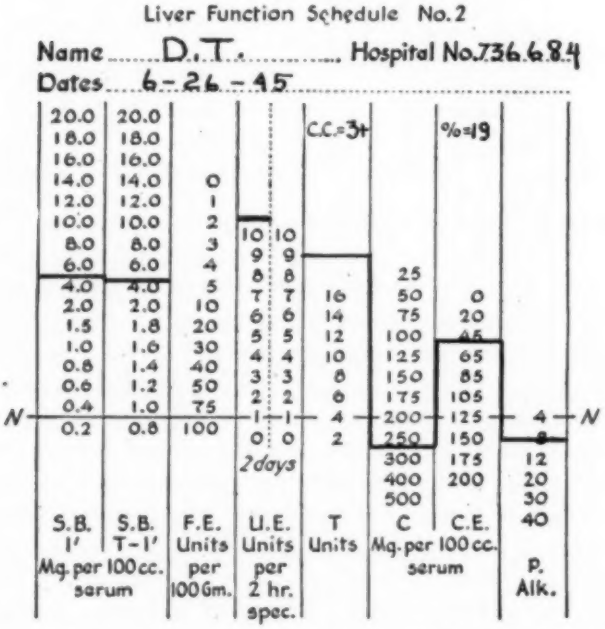

FIG. 8b. *Case 2.* Laboratory studies at time of second admission with relapse.

Liver Function Schedule No. 1

Name D.T. Hospital No 736 684

Dates 6-1-46

H= 0		CC.= 0					
				10 10		
2.0	2.6			9 9		400
1.8	2.4			8 8	10	350
1.6	2.2	16	35	7 7	9	300
1.4	2.0	14	30	6 6	8	250
1.2	1.8	12	25	5 5	7	200
1.0	1.6	10	20	4 4	6	175
0.8	1.4	8	15	3 3	5	150
0.6	1.2	6	10	2 2	4	125
N 0.4	1.0	4	5	1 1	3	100 N
0.2	0.8	2	0	0 0	2	75
0.0	0.4			2 days	1	50
					0	25
S.B. 1' Mg. per 100 cc. serum	S.B. T-1'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.

FIG. 8c. *Case 2.* Laboratory studies 10½ months after apparent recovery.

Liver Function Schedule No. 2

Name K.W. Hospital No.

Dates 5-3-45

			20	CC.=tr.		%=	
20.0	20.0						
18.0	18.0						
16.0	16.0						
14.0	14.0	0					
12.0	12.0	1					
10.0	10.0	2	10 10				
8.0	8.0	3	9 9				
6.0	6.0	4	8 8		25		
4.0	4.0	5	7 7	16	50	0	
2.0	2.0	10	6 6	14	75	20	
1.5	1.8	20	5 5	12	100	45	
1.0	1.6	30	4 4	10	125	65	
0.8	1.4	40	3 3	8	150	85	
0.6	1.2	50	2 2	6	175	105	
N 0.4	1.0	75	1 1	4	200	125	4 N
0.2	0.8	100	0 0	2	250	150	8
			2 days		300	175	12
		179			400	200	20
					500		30
S.B. 1' Mg. per 100 cc. serum	S.B. T-1'	F.E. Units per 100 Gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E.	40 P. Alk.

FIG. 9. *Case 3.* Laboratory studies in case of prolonged epidemic hepatitis.

illustrates a rather striking degree of dissociation in the evidence of liver injury (figure 9). The urine Ehrlich was very high, but the Hanger test and the thymol turbidity were consistently negative. The phosphatase was moderately increased. Unfortunately, the cholesterol esters were not determined. From a differential diagnostic standpoint, the urine Ehrlich was most helpful in this instance since the Hanger test and the phosphatase were both more suggestive of an extrahepatic biliary obstruction. A large amount of urobilinogen in the urine, together with a history of exposure, and a rather marked tenderness of the liver, permitted the correct diagnosis. The patient subsequently made a complete recovery.

The fourth case (E.S. ♀, 38) is another example of a dissociation of liver functional derangement. When first seen, this patient had marked jaundice and severe pruritus. As noted in the first composite study shown in figure 10a, there was no urobilinogen in the urine at this time, and the patient

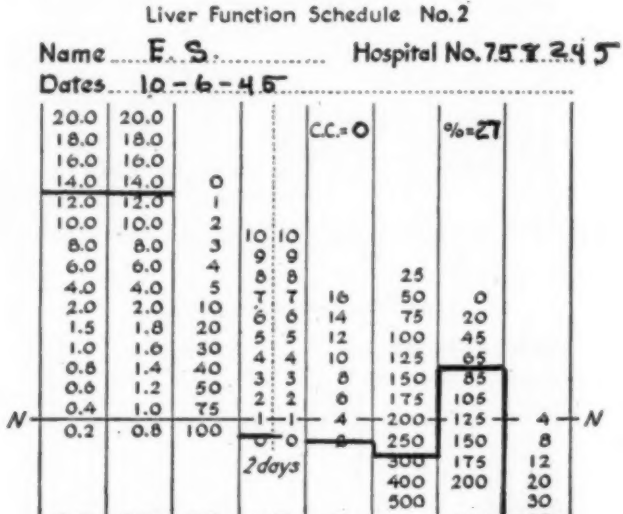

FIG. 10a. *Case 4.* Laboratory studies at time of admission. In figures 10a and 10b the values for the alkaline phosphatase are expressed in King-Armstrong units. (The Bodansky method could not be used at this time due to unavailability of Elon.)

probably had a rather complete exclusion of bile from the intestine, although this was not proved by means of the feces Ehrlich determination, which ought to have been done but was omitted. The high total cholesterol and the very high phosphatase were more suggestive of an extrahepatic biliary obstruction, but the finding that the cholesterol esters were only 27 per cent pointed somewhat more toward a diffuse hepatocellular functional disturbance. In other words, while the total cholesterol and the phospha-

tase values indicated cholangiolar regurgitation of bile and would have failed to differentiate between extrahepatic obstructive jaundice and cholangiolitic hepatitis, the low percentage of cholesterol esters supported the latter diagnosis, since this finding pointed clearly to a concomitant, diffuse hepatocellular injury. The composite study of the second period, as shown in figure 10b, reveals a lessening intensity of jaundice, the presence of increased uro-

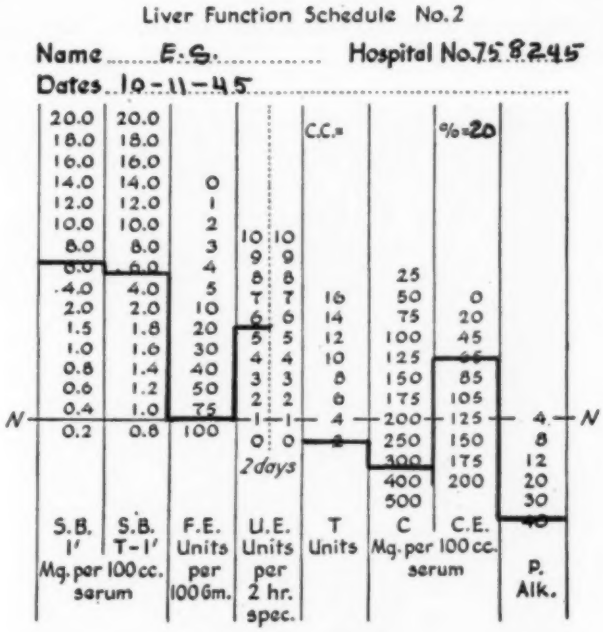

FIG. 10b. *Case 4.*

bilinogen in the urine indicating a resumption of bile flow into the intestine. The lack of qualitative abnormality of the serum proteins is evidenced by the negative Hanger test and normal thymol turbidity. It may be noted that if one had employed only the cephalin flocculation, the total cholesterol and the alkaline phosphatase determinations, one would unquestionably have been misled in the direction of a simple obstructive jaundice and an unnecessary and even hazardous surgical procedure. This emphasizes again the value of a composite study. As has been noted, the patient complained bitterly of pruritus, and was literally covered with excoriations. The blood bile acid determination by Josephson's method [38] revealed an elevation to 4.0 mg. per 100 c.c., or about eight times the normal. This is mentioned only because there is much reason to believe that the bile acid level in the blood is correlated in some way with the degree of pruritus in cases of jaundice. In our experience, the bile acids, total cholesterol and alkaline phosphatase are usually elevated in rather similar fashion, and there is reason to believe that this elevation is a direct manifestation of regurgitation of bile

into the blood; in other words, of regurgitation jaundice. Another question that deserves consideration in this regard, is whether in such instances there may perhaps be an actual over production of phosphatase in the liver, possibly even in the cholangiolar epithelium. We consider this possibility simply because the values that are seen in these instances are often so high that one is led to doubt that all of the increase is due simply to regurgitation of a normal, or relatively normal bile.

The liver biopsy in case 4 revealed evidence of but a mild, although quite definite cholangiolitic hepatitis. The portal spaces contained a con-

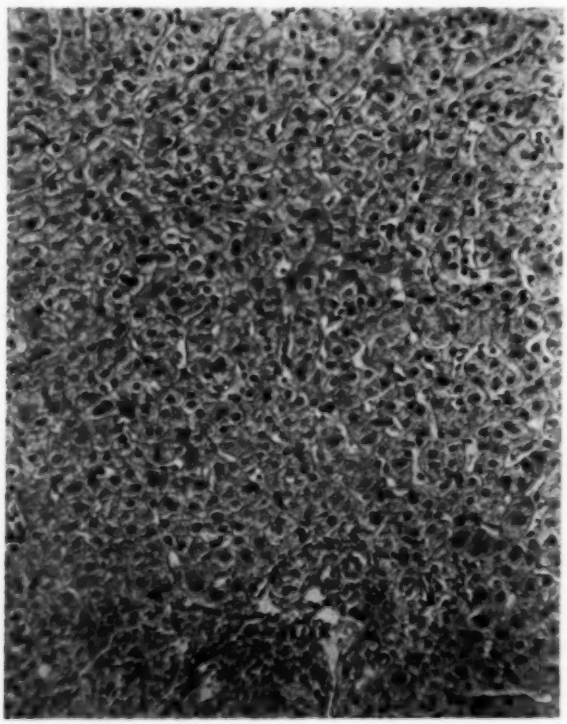

FIG. 10c. *Case 4.* Photomicrograph × 175. Stained microscopic section of liver biopsy secured October 30, 1945 at time of peritoneoscopy. (See text.)

siderable number of mononuclear leukocytes and a small number of neutrophiles (figure 10c). Occasional necrotic liver cells surrounded by leukocytes, were observed. A few bile thrombi were seen. The lack of evidence of obstruction in the intrahepatic biliary tract lends support, as it has in other instances, to the belief that the regurgitation of bile is due to a functional injury and increased permeability of the cholangiolar epithelium.

Case 5 (A.G. ♂, 21) is an example of a chronic active hepatitis with previous jaundice, in which a thorough examination of liver function by ordinary methods failed to reveal anything of significance, although there

could be little doubt even from the clinical standpoint that the patient was having continued activity of his disease. This case was that of a male of 21 years who suffered from a severe attack of (sporadic) hepatitis with jaundice between October 20 and January 1, 1945. In March, 1946 nearly three months after disappearance of jaundice, the liver was enlarged and tender, and the spleen was easily palpable. A biopsy of the liver at this time revealed definite evidence of an active hepatitis consisting of periportal lymphocytic infiltration, occasional abnormal liver cells, and some small areas of actual necrosis (figure 11a).

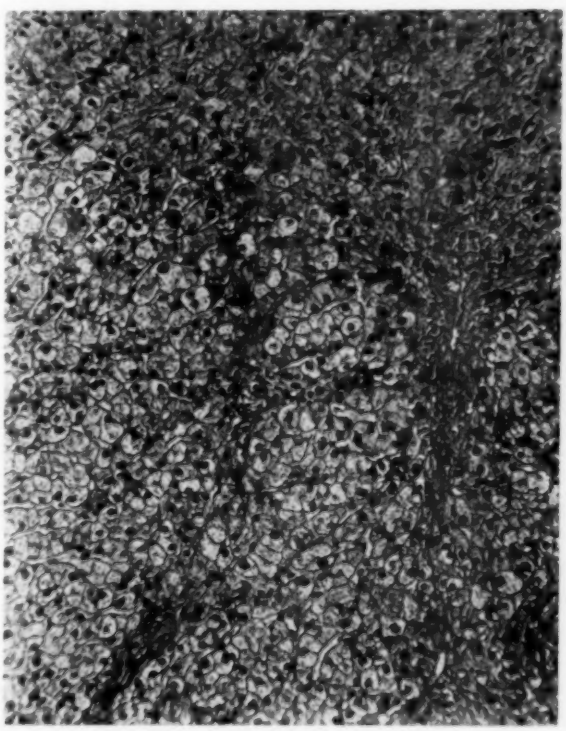

FIG. 11a. *Case 5.* Photomicrograph × 175. Liver biopsy secured March 14, 1946 at time of peritoneoscopy.

In this case, surprisingly enough, the tests in all three liver function schedules were within normal limits (figures 11b, 11c and 11d), with exception of the 24 hour urine urobilinogen and coproporphyrin (figure 11b). This case represents one of the exceptions in which the serial urine Ehrlich reaction on single samples was normal, but the 24 hour urine urobilinogen was distinctly elevated. This means simply that one cannot place a blind reliance on single urine samples, or samples collected for a small fraction of the 24 hour period. While, as previously stated, it is usually true that abnormal amounts of urobilinogen, if any, are excreted in the late morning or

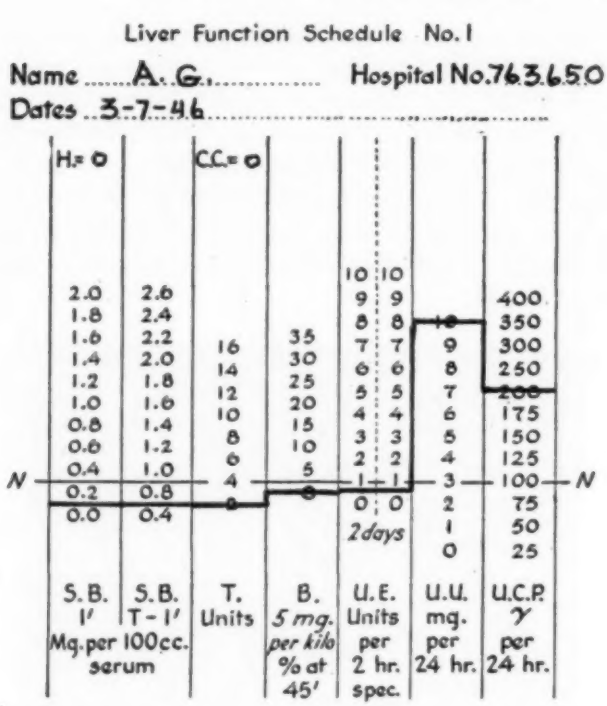

FIG. 11b. *Case 5.* Laboratory studies three months after disappearance of jaundice.

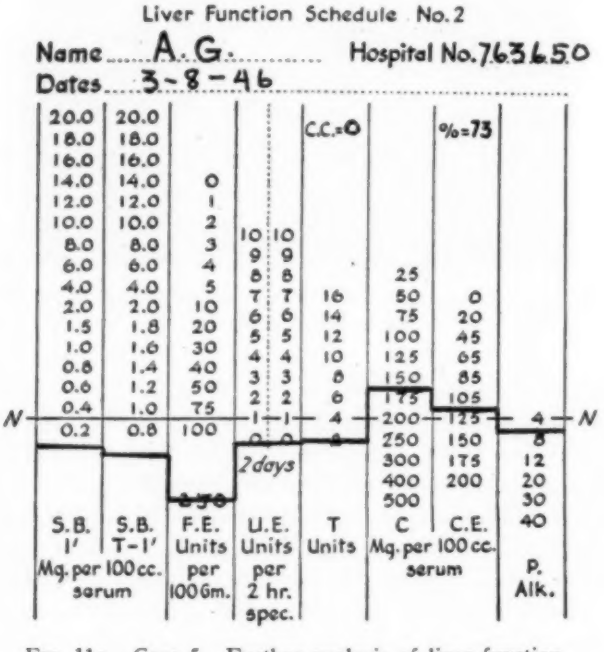

FIG. 11c. *Case 5.* Further analysis of liver function.

afternoon, it is evident from the present example that there are exceptions in which the excessive urobilinogen is excreted at other times during the 24 hours. This case also brings to attention a method of studying liver function to which we have not yet referred, namely, the excretion of coproporphyrin in the 24 hour urine. This will be discussed in detail in a separate communication,[39] and it will suffice to say here that it is a method which is proving of considerable value in the detection of latent liver damage, residual

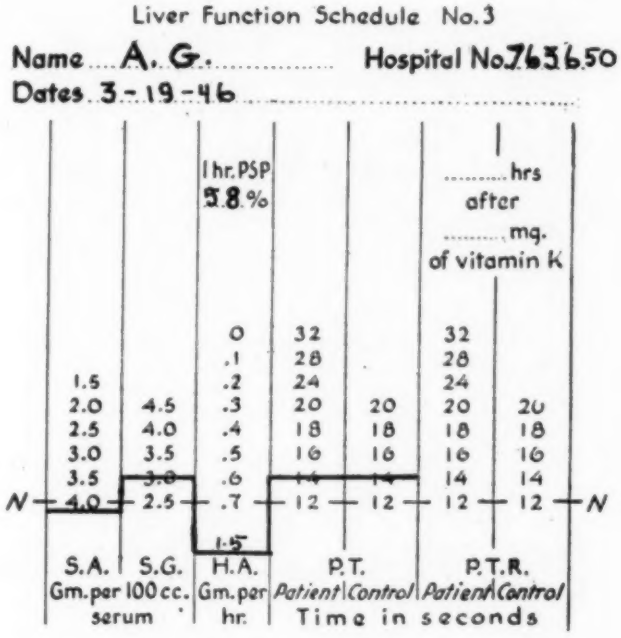

FIG. 11d. *Case 5.* Supplementary studies of liver function.

or chronic hepatitis, and early cirrhosis. There are other causes of elevation of the urine coproporphyrin, such as heavy metals, and chemical poisons, and in interpreting the results, one must, therefore, relate the findings to the history and to other features that may be present in any given case. The present case (figure 11b) is an example of the value of the procedure in late stage or chronic residual active hepatitis.

Case 6 (G.C.Z. ♂, 32) is an instance of chronic hepatitis of even longer duration, the patient having had his initial attack of jaundice over a year previously. Persistent bromsulfalein retention had been noted elsewhere. A biopsy was not done in this case, and the possibility of an early cirrhosis cannot be excluded, especially inasmuch as a number of spider nevi were observed on the skin. As noted in figure 12 the thymol turbidity, bromsulfalein, urine Ehrlich, and urine coproporphyrin were all elevated, somewhat over a year following the initial attack.

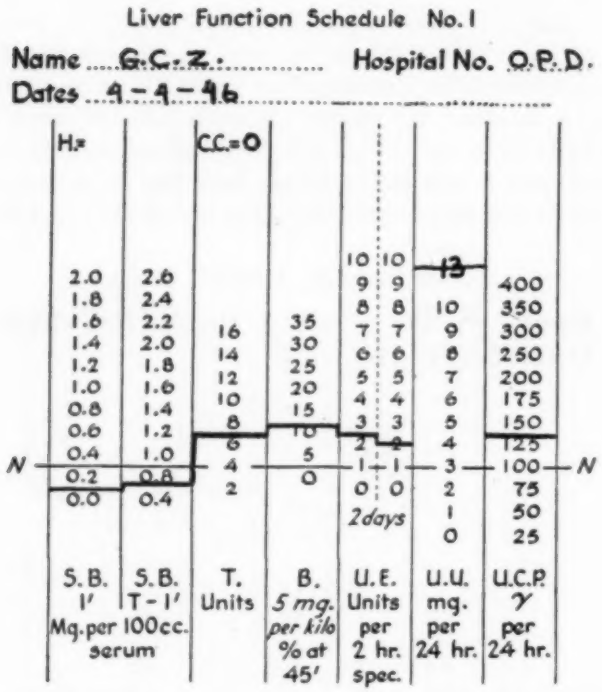

FIG. 12. *Case 6.* Laboratory studies one year after initial attack.

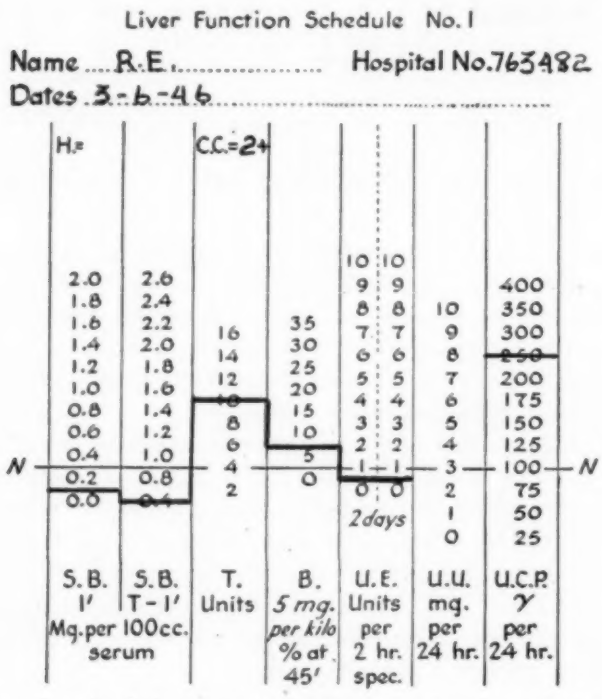

FIG. 13a. *Case 7.* Laboratory studies three months after initial attack.

Case 7 (R.E. ♀, 38) had suffered from what appeared to be a typical attack of infectious hepatitis, three months previously. In figure 13a it is seen that the proteins were qualitatively abnormal and the bromsulfalein slightly elevated, the urine coproporphyrin considerably elevated, while the serum bilirubin and urine Ehrlich tests were normal. Although not shown here, the cholesterol esters were also well within normal limits. The biopsy revealed an outspoken cirrhosis of the liver (figure 13b). Since this patient

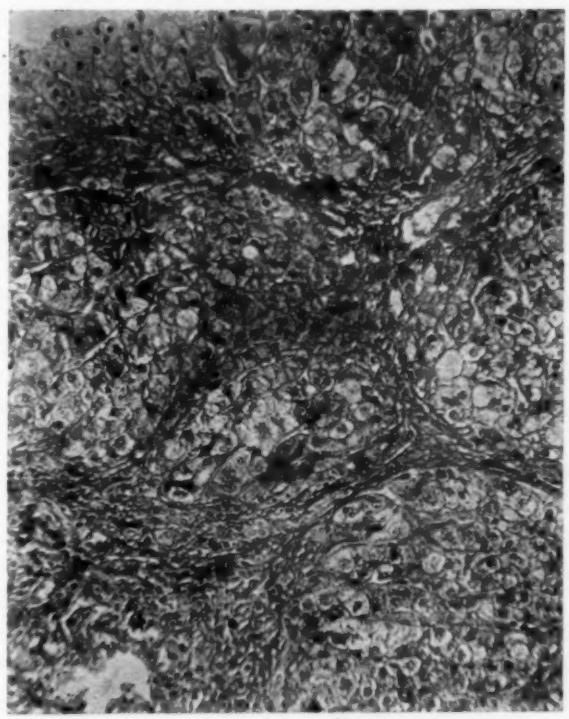

FIG. 13b. *Case 7.* Photomicrograph × 175. Needle biopsy of the liver secured with Vim-Silverman needle March 8, 1946.

had not exhibited any previous signs of liver affection, it is believed that she represents an example of chronic hepatitis undergoing transition to cirrhosis of the liver. This is but one of a number of such transitions that we have had opportunity to study, and which are discussed in more detail elsewhere.[4a, 40, 41]

Figure 14 presents a composite chart of the usual course of events in infectious hepatitis as regards those liver function studies believed to be of most value. Points which may be reëmphasized here are (a) the early appearance of bilirubin in the urine together with an early rise of the one minute or prompt reacting bilirubin; (b) an early disappearance of bilirubin from the urine at a time when the serum bilirubin, both prompt and delayed,

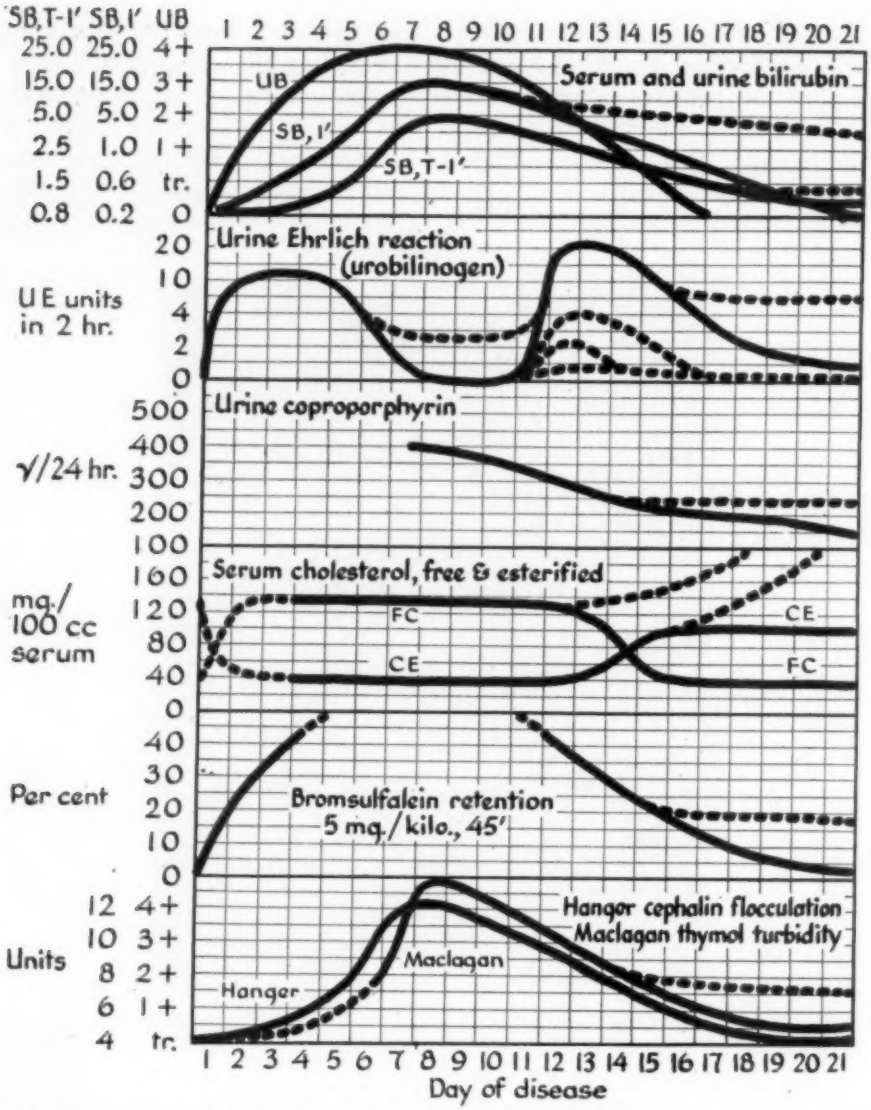

FIG. 14. A composite study of liver function in the different stages of the usual or typical case of infectious hepatitis.

is still distinctly elevated; the broken line indicates the much slower defervescence of jaundice observed in some cases, especially those of the cholangiolitic type; in some of these cases, in fact, the jaundice may persist at the same level for months or years; (c) the early positivity of the urine Ehrlich reaction with a characteristic diminution or disappearance during the height of jaundice. The return of urobilinogen to the urine usually heralds beginning improvement, but as noted, the increase in some cases is transitory or not more than slight. The persistence of a positive urine

Ehrlich reaction is believed to indicate that the disease is still active. (d) The same is thought to be true for a persistent elevation of the urine coproporphyrin. Actually the broken line in this instance is more nearly representative of the majority of cases. On the basis of present evidence, which will be discussed in detail elsewhere, the urine coproporphyrin is one of the last to return to normal. (e) From the available information, it is probable that the cholesterol ester percentage declines sharply in the early stage of the disease, the finding being well established by the fourth or fifth day.[7, 44] The percentage of esters is usually very low at the time of the peak elevation of the serum bilirubin.[44] (f) Bromsulfalein retention occurs early and rapidly becomes marked. This was emphasized in the studies of Barker, Capps, and Allen in the Mediterranean Theater.[3] Persistent bromsulfalein retention above 5 per cent after the disappearance of jaundice points to the possibility of continued activity or transition to cirrhosis of the liver.[44, 45] (g) On the basis of our own experience, the cephalin flocculation and thymol turbidity tests agree very well in most cases of hepatitis, although not so well in certain cases of cirrhosis and other affections of the liver. Based on the available evidence, these tests usually do not become positive as early as the others shown. According to Neefe,[46] the Hanger test usually becomes positive before the thymol turbidity. The data of Watson and Rappaport [42] together with further experience in this laboratory, revealed good agreement between the two tests in the defervescent stage of the disease, although occasional instances were noted in which the thymol turbidity was persistently positive after the cephalin flocculation had become negative. Hanger [43] and Hoaglund [47] have observed this with greater frequency, but this difference may be more apparent than real, since both of these investigators used other methods of recording the degree of turbidity than that employed by Maclagan,[34] and by Watson and Rappaport.[42] The question has arisen as to whether the test may be positive as an evidence of immune response, in other words, representing an elaboration of globulin elsewhere than in the liver cells. This question cannot be answered at present, but it has become clear that the test is specific for a certain type of globulin, or globulin lipid complex [34, 35] as it is commonly negative in other diseases associated with hyperglobulinemia.

Finally, it might be well to recapitulate briefly in regard to the procedures believed of most value in the study of liver function in hepatitis. These may be divided into three groups: (1) The incipient or pre-icteric stage: the serum bilirubin, especially the prompt reacting type, the urine bilirubin, and the urine Ehrlich reaction for urobilinogen; (2) the icteric stage: the Hanger and Maclagan tests for abnormal serum proteins, the serum cholesterol, free and esterified, and the urine Ehrlich reaction followed seriatim; (3) the late defervescent stage: the serum bilirubin, especially the delayed reacting type, the urine Ehrlich reaction, the Hanger and Maclagan tests, the bromsulfalein test, 5 mg. per kilo. at 45 minutes, and the 24 hr. urinary urobilinogen and coproporphyrin.

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THE CLINICAL MANIFESTATIONS OF SICKLE CELL ANEMIA *

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In 1910 J. B. Herrick [1] first reported the association of sickle shaped erythrocytes with severe anemia and certain clinical symptoms now recognized as the clinical entity termed sickle cell anemia. In 1923 and 1924 Sydenstricker [2, 3] and Huck [4] pointed out its relative frequency. There have been many subsequent articles concerning various features of this disease, but it was thought worthwhile to report the general clinical manifestations as observed in the present series of cases. During the period January, 1936 to January, 1946 there were 48 cases of active sickle cell anemia treated in the medical wards of Kings County Hospital. The clinical manifestations tabulated in this article were those demonstrated by these patients. All patients with sicklemia without active sickle cell anemia have been eliminated.

Race: All the patients were of the negro race.

Age: The ages given in table 1 are those at the time of the first admission to the hospital and of the start of symptoms as well as could be determined from the charts.

Table I

Age	On Admission	At Onset of Symptoms
0– 4 years	11 cases	15 cases
5– 9 years	6 cases	9 cases
10–14 years	8 cases	5 cases
15–19 years	11 cases	4 cases
20–24 years	4 cases	2 cases
25–29 years	5 cases	
30–34 years	1 case	
35–39 years	2 cases	

Duration: The duration of symptoms was very difficult to estimate. Histories varied on different admissions even when they were obtained from the same informant. In this article the indications for estimating duration of disease were (1) a known previous diagnosis of sickle cell anemia, (2) a history of pains suggestive of crisis or a history of rheumatic fever, and (3) a history of ulcers of the legs without other known cause. With these points in the past history the demonstration of active sickle cell anemia during hospitalization was considered to indicate that the previous symptoms were also due to the disease. It is realized that this is a very uncertain method. In many cases the histories were so uncertain that no attempt was made to establish the duration of symptoms.

Sex: There were 24 males and 24 females.

Siblings: In five cases there was a brother or sister known to have active sickle cell anemia. In addition there were two cases with a questionable history of a brother or sister with this disease. In three of the five cases

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there was a history of two brothers or sisters with active sickle cell anemia. At one time there were twins, age one year, in the ward both of whom had active manifestations of the disease.

TABLE II

Duration of Symptoms Possibly Due to Sickle Cell Anemia

Diagnosed on admission	11 cases
Duration less than 5 years	11 cases
Duration more than 5 years and less than 10 years	6 cases
Duration more than 10 years and less than 15 years	4 cases
Duration more than 15 years and less than 20 years	4 cases

Temperature: It was striking that practically all the patients manifested fever at one time or another. The great majority of the patients had an elevation of temperature during most of their hospital stay, even when they were asymptomatic.

TABLE III

Highest Temperatures Recorded for Each Patient

Under 98°	1 case
98 to 99°	5 cases
99 to 100°	7 cases
100 to 101°	14 cases
101 to 102°	7 cases
102 to 103°	4 cases
103 to 104°	8 cases
104 to 105°	2 cases

Pulse: A tachycardia was the usual manifestation. The pulse of some infants was not recorded.

TABLE IV

Highest Pulse Rate Recorded for Each Patient

Pulse Rate Per Minute	
Under 70	2 cases
70 to 80	1 case
80 to 90	6 cases
90 to 100	9 cases
100 to 110	2 cases
110 to 120	7 cases
120 to 130	1 case
130 to 140	0
140 to 150	0
150 to 160	3 cases

Blood Pressure: The highest blood pressure recorded was systolic 135 mm. Hg and diastolic 80 mm. Hg. This patient showed evidence of nephritis.

Chief Complaint and Associated Prominent Symptoms or Signs: The 48 patients had a total of 129 admissions during this period of 10 years. The chief complaint was that symptom or sign which caused the patient to seek admission to the hospital. The associated prominent symptoms or signs were those of major importance to the patient at the time of that particular

admission. There were many other symptoms or signs not listed because they were not considered major by the patient during this particular admission. At another admission they might be listed as the chief complaint. Some admissions were during an asymptomatic stage for transfusion or plastic operation for ulcer of the leg. In that case no chief complaint is listed.

TABLE V

Chief Complaint and Associated Prominent Symptom or Sign

	As Chief Complaint	As Associated Prominent Symptom or Sign
Joint or extremity pain	32 admissions	17 admissions
Abdominal pain	22 admissions	3 admissions
Ulcers of the legs	12 admissions	4 admissions
Common colds	9 admissions	0
Neuropsychiatric	8 admissions	5 admissions
Weakness	6 admissions	4 admissions
Dyspnea	4 admissions	8 admissions
Swelling of the abdomen	4 admissions	0
Severe epistaxis	2 admissions	2 admissions
Swelling of the legs (no ulcers)	1 admission	4 admissions

TABLE VI

Findings on Physical Examination

Jaundice	14 cases
Enlarged liver	19 cases
Enlarged spleen	19 cases
Enlarged heart	24 cases
Murmurs of the heart	
systolic—apex	35 cases
systolic—pulmonic area	10 cases
systolic—aortic area	3 cases
systolic—apex and pulmonic areas	8 cases
systolic—apex and aortic areas	3 cases
diastolic—apex	15 cases
diastolic—aortic area	3 cases
Ulcers of legs or scars with history of ulcers of legs	12 cases
Enlargement of lymph glands	
cervical	18 cases
axillary	9 cases
inguinal	8 cases
epitrochlear	1 case
general enlargement	1 case
Fundus oculi (5 cases examined)	
normal vessels	2 cases
tortuous vessels	3 cases

Ulcers of the Legs: There were 12 cases on whom ulcers of the legs or scars with histories of ulcers of the legs were observed during their hospital

TABLE VII

Ulcers of the Legs or Scars with a History of Ulcers

Age on admission	
10–14 years	1 case
15–19 years	5 cases
20–24 years	1 case
25–29 years	2 cases
30–34 years	1 case
35–39 years (both 37 years)	2 cases

stay. On several other cases scars were found, but there was no history of ulcers and they may have been traumatic. The youngest patient with ulcers of the legs was 11 years of age.

Other Findings of Interest: There were a number of other findings not listed above. Some are pertinent to this disease and will be discussed in the comment.

TABLE VIII

Other Findings of Interest

Mental deficiency	7 cases (3 referred to mental institutions)
Priapism	1 case
Salmonella infection	2 cases
Salmonella osteomyelitis	1 case
Turricephaly	2 cases
Meningitis-pneumococcus type XII	1 case (recovered)
Nephritis	2 cases
Pregnancy (7½ mos. stillbirth)	1 case
Congenital cataracts	1 case
Lymphogranuloma inguinale	1 case
Venereal warts	1 case
Abnormal electrocardiogram other than prolonged P-R interval	1 case

Roentgenograms of the Bones and Skulls: About 85 per cent of the roentgenograms of the skull and about 57 per cent of the roentgenograms of the long bones demonstrated changes compatible with sickle cell anemia. In addition there were changes suggestive of blood dyscrasia in the ribs (two cases) and the ilium (one case).

TABLE IX

Report of Roentgenograms of the Bones and/or Skull: Total 29 Cases

Skull: Normal	14 cases
Changes present	12 cases
Long bones: Normal	14 cases
Changes present	8 cases
Ribs: Normal	no reports
Changes present	2 cases
Ilium: Normal	no reports
Changes present	1 case

Roentgenograms of Heart: There were 28 patients concerning whom there was mention of the size and shape of the heart in the reports of their roentgenograms. Of these there were 24 who were found to have evidence of cardiac enlargement. In four cases the heart was reported not to be enlarged. In three cases the condition of the lungs was reported with no mention of the heart. It was not stated whether this was due to technical difficulties or lack of abnormality. Esophograms with barium demonstrated retrodisplacement of the esophagus compatible with enlargement of the auricle in two cases. One of these cases was also interpreted as demonstrating elevation of the left main bronchus. In a third case the esophogram was reported as "suggestive of auricular enlargement." All other cases were negative or an esophogram was not done.

Electrocardiograms: There were electrocardiograms reported for 20 cases. Only one showed any abnormality other than prolongation of the P–R interval. In this case the P–R interval was 0.16 sec., there was slurring of the QRS waves, and the T waves were of low voltage in all leads reported. She was a 10 year old girl admitted to the hospital because of an abdominal crisis. There was a history of a transient, painless paralysis of both of her legs for three weeks at six years of age. Examination revealed: pallor; cervical and axillary glands enlarged; heart, enlarged, coupled beats present, systolic murmurs at the pulmonic and apical areas with an inconstant apical diastolic or presystolic murmur. Once there was a report of a questionable murmur of aortic insufficiency; pulmonic second sound was accentuated. Liver described as four fingers'-breadth below the costal margin; spleen described as "down to the iliac crest." Skull and long bones reported normal on roentgen-ray examination. Blood count: hemoglobin 6 grams, erythrocytes 1,600,000, leukocytes 40,000, polymorphonuclears, 70 per cent, 140 nucleated erythrocytes per 75 leukocytes. Icteric index 4.5 units. Sedimentation rate 6 mm. per hour. Report of roentgenogram of the heart: enlarged, mitral contour, hypervascularity of the lung fields. No enlargement of the auricle demonstrated by esophogram. Two facetted gall stones were seen. There were four separate admissions. At the time of her last admission she was complaining of dizziness and pains in her knees of one week's duration. However, this was the only history obtained of pain in her extremities. The only electrocardiogram had been taken during a previous admission.

TABLE X

Report of Electrocardiograms—P-R Intervals and Ages

P-R Interval	Age	P-R Interval	Age
0.12 secs.	10 years	0.16 secs.	17 years
0.14 secs.	1 year	0.16 secs.	10 years
0.14 secs.	18 years	0.18 secs.	25 years
0.14 secs.	25 years	0.18 secs.	27 years
0.14 secs.	30 years	0.18 secs.	23 years
0.14 secs.	3 years	0.18 secs.	14 years
0.14 secs.	6 years	0.20 secs.	
0.16 secs.		0.20 secs.	10 years
0.16 secs.	11 years	0.20 secs.	
0.16 secs.	14 years	0.23 secs.	16 years
0.16 secs.	4 years		
0.16 secs.	3 years		
0.16 secs.	19 years		

Blood Counts: The leukocyte counts are uncertain as the number of nucleated erythrocytes was often large, and the corrected count is probably much lower in those cases with very marked leukocytosis. There were only four blood counts with leukocyte counts below 10,000, and there were 8 leukocyte counts over 30,000. In general there was a moderately severe anemia with a definite leukocytosis, usually without much increase in the percentage of polymorphonuclear leukocytes.

Reticulocyte Counts: There were too few reticulocyte counts to be of any statistical value. Those reported were all elevated.

Icteric Index: There were many reports of elevation of the icteric index. There were only 10 cases with an icteric index of 5 units or below, and for seven of these other tests were all above normal. There were four reports of

TABLE XI
Blood Counts

	Lowest	Average	Highest
Hemoglobin	3 grams	6.7 grams	12 grams
Erythrocytes	1,000,000	2,508,000	5,180,000
Leukocytes	5,700	19,382	52,000

over 100 units, the highest being 280 units. Some of these high values will be discussed in the comment.

Deaths: There were four deaths with three autopsy reports which will be discussed in a subsequent article.

COMMENT

Several interesting observations are emphasized by this report. One is the frequency of abdominal pain. Many times this complaint was a difficult problem as has been reported by others.[5] Many diagnoses were considered, including renal colic, acute salpingitis, acute appendicitis, and acute cholecystitis. None of these patients was submitted to operation for abdominal pain.

Mental Deficiency: The frequency of mental deficiency is surprising. This diagnosis was made on the basis of clinical observation only, but was borne out by the admission of three of these patients to mental institutions. Although many authors have reported neurological manifestations,[6, 7, 8, 9] mental deficiency was not emphasized as a feature of this disease. Other findings included localized paralyses, signs of meningeal irritation, dizziness, headaches, drowsiness, convulsions, and choreiform movements. Probably future attention to neuropsychiatric manifestations will reveal that cerebral lesions are more common than is generally realized.

Priapism: One patient developed priapism. There have been several reports of priapism due to sickle cell anemia, but [10, 11, 12] it is believed that this is the first case reported which was relieved by 150 R.U. of roentgen therapy to the penis. No data are available as to later developments in this case.

Pregnancy: This report includes a 17 year old female who was first admitted when she was six months' pregnant. At that time she gave a history of pain in her joints with dyspnea and palpitation of five years' duration, and abnormal movements of her body for a few hours. At physical examination there were choreiform movements of her extremities, but she signed her

release and left the hospital. She was readmitted when she was seven and one-half months' pregnant. At that time she was complaining that for 24 hours she had severe pains in her arms with fever. Examination revealed an icteric tinge to her sclerae, enlargement of her cervical lymph nodes, no clinical enlargement of her heart, but there was a systolic murmur at the apex of her heart, and once a presystolic murmur was heard in the same area. The liver and spleen were not palpable. There were scars on both of her legs. The uterus was the size of a seven and one-half months' pregnancy. Blood count: hemoglobin 6.8 grams, erythrocytes 2,600,000, leukocytes 18,300 (corrected to 12,200), 100 per cent sickling of the blood smear after 24 hours; icteric index 18 and 22 units, van den Bergh direct delayed, faint trace; electrocardiogram was normal (P–R interval 0.16 sec.). After a few days she developed a severe abdominal crisis which continued for several days and did not cease for some time after she suddenly delivered a still born male child.[13]

Heart: It is interesting that examination by roentgen-ray revealed cardiac enlargement in 50 per cent of the total cases of this series. Only four or possibly seven cases had no demonstrable cardiac enlargement. It is unfortunate that all cases did not have a roentgenogram of the heart. The reports of enlargement of the left auricle by esophogram are unusual.[14] None of the autopsies revealed valvular damage or myocardial evidence of rheumatic fever.[14, 15]

Electrocardiograms: There were five cases which were considered to have prolongation of the P–R interval. Quite possibly more frequent electrocardiograms would have demonstrated more cases with a prolonged P–R interval.[14, 15]

Roentgenograms of the Bones and Skulls: Sometimes these changes in the osseous system were scanty and sometimes marked, but all cases suggested blood dyscrasia to the roentgenologist. Several reports [16, 17] of these bone changes are available. No unusual change, not already described, was found.

Icteric Index: The icteric index was very variable even in the same patient during the same admission. The two highest, 150 and 280 units, were reported for different patients. The first of these patients was considered to have a hepatitis. The urine was strongly positive for bile; urobilinogen was present; stools were negative for bile; van den Bergh was direct delayed, faint trace; serum bilirubin was 19 mg. per 100 c.c. All symptoms and signs gradually subsided.

The second case also demonstrated a strongly positive test for bile in the urine with urobilinogen present. The stools were negative for bile; serum bilirubin was 10.1 mg. per 100 c.c. A gall-bladder series did not reveal any calculi, but the gall-bladder shadow was faint, and failed to evacuate after a fatty meal. These were both undoubted cases of active sickle cell anemia. Diagnoses of hepatitis and cholecystitis are difficult to prove or disprove without operation or autopsy.[18, 19]

Liver and Spleen: One of the most striking features of this study was the marked, rapid changes in size of both the liver and spleen. During the same hospital stay the spleen might be reported as "not palpable," and then "increased to the iliac crest." The liver might suddenly increase in size until it was described as palpable three or four fingers'-breadth below the costal margin. Recession of both organs could also be rapid. Usually during the period of rapid increase in size there would be a notation of abdominal pain with tenderness of the involved organ, but tenderness and pain were not always reported. After subsiding they could sometimes again increase in size. In general the very large spleens were in patients less than 10 years of age, but there was one girl, 19 years of age, with a spleen "enlarged to the umbilicus" who had complained of pain in her legs "all her life." For three years prior to admission she had ulcers of her legs. Four skin grafting operations were performed.

Summary

The clinical manifestations of 48 cases of active sickle cell anemia are noted and tabulated. All patients with sicklemia without active symptoms have been eliminated.

The previous concepts of the clinical features of this disease are confirmed, but particular attention is directed to the frequent occurrence of the following manifestations: (1) cardiac enlargement, (2) the presence of diastolic as well as systolic murmurs of the heart, (3) prolongation of the P–R interval, (4) roentgenographic changes in the osseous system, (5) rapid and marked changes in the size of the liver and spleen, (6) neuropsychiatric signs and symptoms especially mental deficiency, and (7) abdominal crises.

Two unusual manifestations were the demonstration by esophogram of auricular enlargement in two cases, and the relief of priapism by roentgen therapy.

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HISTAMINE IN THE TREATMENT OF PEPTIC ULCER *

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CRUVEILHIER in 1829 said "ulcer of the stomach is surrounded by profound obscurity, and one wonders why a single place in the stomach is deeply affected and all the other parts of the organ are in a state of perfect integrity." Since that date many investigations have been devoted to the study of both the etiology and treatment of ulcer, and have led to numerous arguments and conflicting opinions. The attempts to determine the etiology of peptic ulcer have failed to yield any convincing results. Others have attempted to prevent the development of experimental ulcers by psychological, endocrine or chemical means, particularly by attacking what, in our opinion, seems to be the normal gastric medium of the ulcer patient, *his* acidity. A great many have accepted the view, as expressed by Palmer,[1] that the continued secretion of an abundance of a highly acid juice constitutes the greatest hindrance to healing, or at least that acid is irritating to the ulcer (Sandweiss [2]), and that it contributes to the development of the pain of ulcer (Quigley [3]).

Others have seriously questioned this view. Thus Brown and Dolkart [4] observed no significant change in acidity prior to the recurrence of symptoms of ulcer and believe that the degree of free acidity bears absolutely no relationship to the degree of distress. Barford [5] found the acidity higher after treatment than before. The observations (e.g., by Val Dez [6]) that the volume of nocturnal gastric secretion is greatly increased in patients with ulcer has been questioned.[2] Eusterman and Balfour [7] among many others have noted that sodium bicarbonate depresses acidity only momentarily and that in a few minutes this is at least as high as before the medication. Even section of both vagus nerves causes only a temporary arrest of the secretion of acid. They found that patients who developed marginal ulcer had no higher acidity than those who remained free from recurrence. They also state that under favorable circumstances ulcers have healed permanently without treatment by alkalies, and the majority of patients whose duodenal ulcers were permanently cured after gastroenterostomy continued to have more or less free HCl in their gastric secretion.

This illustrates a few of the contradictory observations and views that have been expressed regarding peptic ulcer. The large number of procedures advised and discarded in the therapy of ulcer attests to the confusion on the subject.

Removal of foci of infection has been advocated by some in the belief that there is a relationship between these foci and the production of ulcer.

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Allergy has been noted as a possible cause and investigation of allergens as a method of treatment has been advised.

The drugs suggested for direct action on the gastric mucosa have been numerous. The bismuth salts have been used for decades. Sodium bicarbonate was employed until stopped by the fear of alkalosis without regard to the fact that the gastric acidity rises after a brief depression. Then came the slower acting antacids like the carbonates and the oxides, and more recently the adsorbent, such as the aluminum salts in various combinations. Belladonna and other antispasmodics have been widely acclaimed. In order to counteract the supposedly vicious nocturnal secretion of acid, milk drip and aluminum hydroxide drip were suggested. Mucin and okra mucin were heralded as the "cure" because of their protective properties. A number of substances have been administered by injection: pepsin, parathyroid and insulin as well as various protein products, and more recently histidine. The latter was advised because of the supposed amino-acid deficiency believed to be present in ulcer patients. Pituitary "snuff" was employed for a short period of time. Because patients who become pregnant lose their ulcer symptoms, the urine of pregnant females was searched for some protective substance. This work led finally to the isolation of urogastrone from normal urine. The mucous membrane of the stomach and duodenum then received the investigators' attention with the elaboration of enterogastrone and duodenal extract. Then came hyperalimentation with protein hydrolysates.[8]

The surgeons also have participated in the fight against recurrent gastroduodenal and, as an occasional sequel, marginal ulcer. They began with simple excision and followed with gastro-enterostomy with or without pyloric occlusion, and later employed pylorectomy and pyloroplasty. Then came partial and more recently subtotal gastrectomy with vagotomy, first unilateral and then bilateral. Now the newest procedure to be advised is vagotomy without gastrectomy.

All of these procedures had but one aim: acidity interferes with ulcer healing, and therefore a way must be found to depress or remove the gastric acidity permanently! At this point it suffices to note merely that, regardless of the procedure advocated, ulcer recurrences kept coming and no method has as yet belied the aphorism: "once an ulcer patient, always an ulcer patient." These are but a few of the many questions which must arise in your minds as they do in ours. Why does the ulcer develop almost always on the lesser curvature of the stomach or in the first portion of the duodenum? What prevents the ulcer from growing deeper and wider after it has formed? Why does the anatomic defect persist although the symptoms of ulcer have disappeared? What is the explanation for the typical ulcer syndrome with negative roentgen-ray findings, and nothing found at operation, which nevertheless was occasionally cured by appendectomy? In what manner is the relief from symptoms so frequently obtained, "after-a-while" as the

result of so many varied methods and procedures, or "in due time" without therapy?

No one can as yet explain why recurrent episodes of symptoms of ulcer generally recur in the spring and fall, or at times after an upper respiratory infection, or frequently following an emotional storm or so often for no apparent reason at all.

We have had the impression for many years, that whereas the acid pepsin factor may be important in the as yet unproved etiology of ulcer, there appears to be no relationship between the maintenance of gastric acidity and the disappearance of either the symptoms or of the anatomic defect or of both.

In complete contradiction, therefore, to the implied dictum: "neutralization of acid is necessary for the treatment of peptic ulcer," we have used histamine, a potent acid-stimulating, vaso-dilating agent, by injection over a period of about eight months. We know that it has frequently been suggested that histamine plays a part in the hypersecretion of gastric juice in the patient with an active ulcer. The literature contains many articles on the production of ulcer in animals by the injection or implantation of histamine. In answer to one investigator, who said that "the ease of production of perforating gastric and/or duodenal ulcer in most laboratory animals by the implantation of histamine in beeswax emphasizes the great importance of the acid activity of the gastric juice in ulcer genesis" we should like to say only this: the doses of the drug used in these animal experiments were enormous and were frequently fatal. Horton [9] had occasion to treat 10 patients with histamine headache and peptic ulcer, in whom both the headache and the ulcer crater disappeared after the injections of histamine he used for desensitization.

Brun [10] in 1944, working on the vascular theory, found that injection of adrenalin in ulcer patients produced an increase of pain which was quickly relieved by nitroglycerin or amyl nitrite without change in the intra-gastric tension. He called attention to the work of Jacob and Israel [11] published in the Presse Medicale in 1938, which was first seen by us in March 1946, five months after we had started our study. These investigators reported complete relief from ulcer symptoms in all of 17 cases, using daily injections of 0.1 mg. of histamine. They believed their spectacular results were caused by a change, a relaxation, in the vascular mechanism of the gastro-duodenal area.

In our study we gave an average of 20 daily injections of 0.2 mg. of histamine phosphate to 75 ulcer patients. Except in the few instances in which tincture of belladonna was also used, no other medication was given. Our patients had gastric, duodenal and marginal ulcers. Both sexes were represented, the male predominating in a ratio of about five to one, of whom three males were colored. Some had had one or more hemorrhages just prior to, or at some time before the start of our treatment. The ages varied

from 21 to 65. A number of the cases showed varying degrees of gastric retention, and most of them had been treated on previous occasions by alkalies and non-specific parenteral protein therapy, and two with protein hydrolysates. Several had had perforations at some time in the past. All came to us because they were in the midst of a recurrence of symptoms of ulcer, the number of previous episodes ranging from 2 to 22. The roentgenologic evidence was positive in almost all the cases, a few giving a typical, classical story of ulcer with negative roentgen-ray findings. They were all placed on a liberal, bland diet with frequent feedings, and tobacco was completely forbidden. (It should be noted, however, that some of the patients continued to smoke in spite of our interdiction.) Gastric analysis was done in a number of the patients, and the usual response to histamine stimulation was noted in most.

We have not seen one untoward reaction, even in those patients who had been given 30 or more injections. Of course we did note flushing and temporary headaches at times, especially in the beginning when we gave 0.5 mg. per dose.

If acid, as has been claimed, is irritating to ulcer, in using this powerful acid-stimulating agent we should have found a marked increase in symptoms in these patients who were in what has been called "the active ulcer phase." However, we appear to have seen the opposite, because in but one single instance were the symptoms aggravated. Of the 75 cases treated, complete relief from pain took place after the fourth injection in 50 or 66 per cent of our cases, and in less than 10 injections, in 62 or 82 per cent. An additional 7 or 10 per cent required 12 to 18 injections before pain relief was obtained and five patients or 6 per cent did not respond, the latter even after we had changed our medication to alkali, belladonna and sedation. One patient developed a fatal perforation and hemorrhage during the treatment, and still another perforated soon after we had begun our injections. Several gastric ulcers disappeared rapidly, one in less than three weeks. Gastric retention was relieved in five cases without the use of belladonna, and one had almost complete relief from his concomitant cardiospasm.

Many of our patients have already remained free from symptoms for a period of months, a few in spite of upper respiratory infections and emotional upsets. Eighteen of these were given a second series of injections in the hope that a recurrence could be prevented. We can report that almost all of these patients, who had previously had two or more episodes per year, have now for the first time in years gone through a spring season completely free from ulcer pain. If this small number of cases is any indication at all, perhaps we have found a way to prevent seasonal recurrences.

It must be remembered that gastric ulcers especially have disappeared spontaneously, or in spite, rather than because of a particular form of treatment (although perhaps not until now in the presence of stimulated gastric acidity). One must not use partial or even complete remission from

symptoms for any length of time as the criterion for "cure," as we have all seen both recurrent episodes and remissions after every conceivable type of medical routine and surgical procedure.

It would appear that we might use but two criteria for the evaluation of the results of therapy. Have we obtained rapid relief from the pain of ulcer and can we prevent the recurrences previously experienced? Our work indicates relief of ulcer pain in a large percentage of our cases with startling rapidity and apparent prevention of recurrence in a substantial number. We believe that our work proves that maintenance of gastric acidity does not interfere with symptomatic relief in any, nor with the disappearance of roentgen-ray evidence in some cases. The mechanism of the pain of ulcer may lie in vascular spasm, and its relief may be the result of a change in the mechanism by the use of histamine, regardless of gastric acidity.

Summary

1. Seventy-five unselected cases of ulcer, with gastric, duodenal and marginal deformities were treated by daily injections of histamine. Only tincture of belladonna was permitted in a few cases.

2. In 66 per cent of the cases, relief of pain took place after the fourth injection, and in 82 per cent after the tenth. Ten per cent of our cases remained unaffected even after 30 injections.

3. The deformities of duodenal and marginal ulcers showed great improvement in some cases, and gastric ulcer was seen to disappear quickly.

4. Twenty-six cases were protected against an anticipated recurrence by seasonal prophylactic injections.

Discussion

One might ask with propriety, where are the controls? Isn't it possible that injections of sterile water might have produced the same effects? Sterile water, however, would not increase gastric acidity nor would it relax vascular spasm and increase splanchnic blood supply. We have given injections of novoprotein, vaccineurin, pepsin, parathyroid and histidine without adequate results.

If one can take a similar series of more than 100 unselected cases of gastric, duodenal and marginal ulcer, many of whom had had previous hemorrhages and some of whom had had perforations, and obtain complete relief from ulcer pain in four out of five in 10 injections; and if one could take 26 of these and repeat the series of injections with sterile water and prevent anticipated recurrence of ulcer, then one would be justified in saying that the acid-pepsin factor as a possible cause for ulcer recurrence and all attempts at the treatment of the recurrences by the decrease or abolition of gastric acidity by any method (ought to be respectfully interred and laid to rest for all time to come) can be permanently dismissed from consideration.

Conclusions

1. Maintenance and even increase of gastric acidity has no bearing on the symptom-complex of ulcer or the disappearance of ulcer deformity.

2. There is no relationship between the continuance of the anatomic deformity and the recurrence of ulcer.

3. The mechanism of the pain of ulcer seems to be vascular and is relieved by the injection of histamine which relaxes vascular spasm and increases splanchnic blood supply.

4. It appears possible to prevent recurrences by prophylactic seasonal injections of histamine.

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CONTINUOUS FEVER OF INTESTINAL ORIGIN *

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No phase of medicine is more fascinating, no problem in the clinical sciences more elusive than the picture of low-grade continuing fever that defies elucidation. Many interesting theses have been written upon this topic, among the most important and recent being those of Hamman and Wainwright [1] in 1936, Kintner and Rowntree [2] in 1934, and of Reimann [3] in 1936. In these various treatises one reads of possible causes of such fever, causes which are recognized in classical medicine, such as tuberculosis, syphilis, rheumatic fever, tularemia, brucellosis, pyogenic infections, bacterial endocarditis, Hodgkin's disease, new-growths, and fevers of psychogenic origin. In none of these thorough and exhaustive papers is there a hint that the intestinal tract may be the site of the causative factor of obscure low-grade fever.

In our clinical experiences we have encountered such cases in which the subjective symptoms of abdominal pain and mild diarrhea have escaped notice and emphasis. We are impelled to call attention to a group of cases in which obscure fever has ultimately been explained by the discovery of benign inflammatory disease in the small or large bowel. Distal or general manifestations have as a rule similarly been ignored or misinterpreted, ocular complications, articular involvement and cutaneous rashes have failed to be appreciated in their relationship to the fever and to the mild diarrhea, the whole making a symptom-complex which is easy to recognize when the significance of the symptoms as a whole is appreciated.

Ulcerative colitis of the non-specific variety is a common source of low-grade fever, and it is recognizable with ease because the severity of the diarrhea, the abdominal pain and the loose fluid movements readily focus attention upon the intestinal tract. The diagnosis is easily verifiable by a sigmoidoscopic examination and a roentgenographic study following a barium enema. Complications in the large or smaller joints of the extremities are not uncommon, the so-called "arthritis dysenterique" and ocular complications and cutaneous rashes are not unusual.

Yet, obvious as such a case should be to an experienced general clinician, we encountered an instance in a young woman who was treated for keratitis and episcleritis with low-grade continuous fever, competent ophthalmologists in charge of the case focusing all attention upon the obvious ocular lesions and failing over a course of years to take into consideration the mild but obvious diarrhea which was not pressed upon their attention. Eventually sight was lost in both eyes owing to corneal opacities resulting from healing keratitic ulcerations. The continuous low-grade fever and the low leukocyte count were readily shown by barium enema and sigmoidoscopy to originate in a severe ulcerative colitis involving the whole of the colon. The ocular manifestations were but complications of the intestinal infection.

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Segmental Colitis: A most characteristic type of low-grade fever of intestinal origin with minimal local symptoms but with maximal general manifestations is often seen in cases of regional or segmental colitis. We speak often of this type of case as "right-sided" colitis because the cecum, ascending and transverse colon are most often involved, whereas the sigmoid and particularly the rectum are spared. The freedom of the rectum and anal sphincters from involvement explains the mildness of the diarrhea, perhaps only two to three stools per day without urgency but accompanied by mild abdominal pain. This type of disease is further notable for systemic manifestations, such as continuous low-grade fever, and a low leukocyte count; and for involvement of large joints such as knee, elbow, wrist, as well as the temporo-mandibular, and the smaller phalangeal and tarsal joints: Notable too are the varied ocular complications, the most common of which are keratitis, corneal ulcerations, phlyctenular conjunctivitis, iritis, and uveitis. The cutaneous manifestations of erythema nodosum and the mucosal involvement in the form of oral aphthous ulcerations may be minimal and easily overlooked.

When, as is usual, the intestinal symptoms of diarrhea and pain are minimal, when the continuous fever and prostration are most noteworthy, and when attention is focused on articular and ocular manifestations, the diagnosis may well go askew. Rheumatic fever is the favorite working diagnosis, bacterial endocarditis, Libman-Sachs disease, and peri-arteritis nodosa are frequently assigned as tentative explanations of the continuous low-grade fever.

A young woman was seen suffering from fever, uveitis and iritis and large swollen joints. The tentative diagnosis was either peri-arteritis nodosa even though eosinophilia and renal manifestations were absent, or disseminated lupus erythematosus without the rash and without cardiac involvement. Throughout the illness the mild diarrhea had been completely overlooked. Eventually the triad of fever, joint involvement and ocular manifestations with an associated diarrhea called for studies to elucidate the cause of the frequent bowel movements. A barium enema readily disclosed a segmental or right-sided colitis. Appropriate treatment of the intestinal infection by chemotherapy and antiseptic lavages led to prompt general recovery, subsidence of fever and rapid amelioration of the ophthalmological manifestations. A similar case, in a young girl, was seen again with low-grade fever, articular manifestations, a corneal ulceration, but in this instance with evidences of an old valvular heart disease in the nature of a mitral insufficiency. The diagnosis of chronic rheumatic heart disease seemed obvious and lesions of the eye and joint as natural complications. All attention was focused on the general manifestations, while the mild diarrhea was completely overlooked. The negative sigmoidoscopy at first discouraged the correct diagnosis, but the barium enema disclosed a typical right-sided or segmental colitis involving the cecum and ascending colon. Again attention to the intestinal infection led to prompt recovery; the corneal ulcer healed readily but unfortunately with a dense opacity obscuring vision in the one eye.

A great many cases of this type of segmental colitis are associated with old valvular heart disease apparently of long standing. The relationship between ulcerative colitis of this type and chronic valvular disease of the heart

will bear greater scrutiny. It may well be that the co-existence of non-specific colitis and rheumatic endocarditis is purely fortuitous in these cases, and yet such a coincidence seems unduly frequent. It would seem that the chronic cardiac involvement occurs more frequently than chronic rheumatic heart disease in the control population for even these climates. Positive blood cultures in ulcerative colitis are not infrequent though the organism found is usually non-specific and is rarely the same bacterium in a successive group of cases. Certain it is that sub-total colectomy cures and removes the colitis and results in subsidence of the active phases of the heart disease with the complete disappearance of all articular manifestations. In most of these cases the low-grade fever subsides when the correct diagnosis is established and attention is focused on the intestinal origin of the infection. Until we meet with our first autopsy in a case of segmental colitis and the heart musculature is serially sectioned for Aschoff bodies, the true relationship of this type of colitis to the heart complications so frequently encountered must remain undecided. The eye and joint complications and the frequent involvement of the heart valves lead to the most common mistake of grouping these cases as chronic rheumatic fever. At times the articular manifestations are so brisk and active that as in one instance the case was referred for study by an orthopedist as one of acute infectious arthritis. The occurrence of a peri-anal abscess for the first time focused attention upon the diarrhea which had been of minimal intensity. The diagnosis of diffuse segmental colitis was readily established by the barium enema. Here medical treatment was unsuccessful in allaying the disease, and operation eventually was required.

When erythema nodosum covers the anterior aspects of the legs and arms the usual diagnosis of rheumatic fever seems well substantiated as part of the low-grade continuous fever, and yet typical erythema nodosum is a very common manifestation of all varieties of ulcerative colitis, it is characteristic of the disease and is moreover a good prognostic sign of eventual recovery.

Regional Ileitis: It is interesting to note how frequently the diagnosis of ileitis is completely overlooked in the absence of severe pain and diarrhea and in the presence of continuous low-grade fever.

Such a typical instance was noted in the case of a 12 year old girl whose previous history was negative, except for scarlet fever. Fourteen months previously she developed fever and mild diarrhea, the stools being loose, not bloody and not accompanied by pain. For three months she had been hospitalized for careful observation, the temperature (oral) ranging between 99.6° and 101.1° F. The sedimentation rate was prolonged, secondary anemia (60 per cent hemoglobin) and a mild leukocytosis (12 to 14,000 white cells) were present. The barium enema was reported as showing an "irritable colon," and all other indications of an intestinal origin of the fever were henceforth dismissed. A working diagnosis of rheumatic fever was retained. She continually lost weight but developed some slight tenderness in the lower right abdomen. A negative sigmoidoscopic report lent renewed assurance to the fact that the diarrhea was inconsequential as the cause of the fever. Belatedly a roentgenographic examination after a barium meal revealed a typical terminal ileitis involving 18 inches of the distal ileum proximal to the ileo-cecal valve. Laparotomy confirmed the findings; a resection of the terminal ileum and ascending colon resulted in an eminently satisfactory cure.

In another case seen within the last month a boy of 17 ran irregular fever, at intervals, for seven years. The strictest cross-questioning elicited only one transient period of diarrhea for a few weeks, followed the remainder of the time by normal daily evacuations or by mild constipation. Any number of tentative diagnoses for the irregularly recurrent fever were suggested, the most prominent one being brucellosis, though all blood agglutination and skin tests were negative. Finally a barium meal was given which revealed a diffuse inflammatory involvement of the upper ileum and the lower jejunum in a granulomatous process. The inability to make the correct diagnosis in this case is readily understandable since in the absence of diarrhea, fistulae, perirectal abscesses or distal joint involvement, there was nothing to focus the attention of the observer on the small or large intestine as a causative focus of infection.

Diffuse ileo-jejunitis presents a baffling clinical picture, which is little known and rarely recognized. Here, except for the mild abdominal pain and minimal diarrhea, there are no distal manifestations, no articular involvements, no ocular symptoms, no internal or external fistulae, no suppurative rectal complications. Only fever of an irregular and continuous type, secondary anemia and progressive loss of weight mark the protracted clinical course.

A young woman 26 years of age had had an appendectomy performed 15 years previously for what appeared to be a classical instance of acute appendicitis, although no pathological examinations were reported at that time. She was well until 13 years ago when she developed erythema nodosum over the anterior surfaces of her legs, a manifestation which was regarded as rheumatic in origin. Three years ago she began to exhibit fever, low-grade, continuous but at times up to 104.6° F. The erythema nodosum recurred, and six months later for the first time she complained of sharp abdominal pain, usually at night, not associated with meals nor with frequent bowel movements. At no time did she have diarrhea; her weight increased rather than diminished. Her blood count was within normal range and agglutination tests for brucellosis were repeatedly negative. After all these varied years of observation the abdominal pain finally centered attention on her intestinal tract. A barium meal disclosed a diffuse ileo-jejunitis involving almost all of the jejunum and the whole of the ileum down to but not including the terminal segments of the small bowel. The entire small intestine seemed converted into one continuous "string sign" traversing the abdominal cavity from side to side in rigid unyielding loops whose mucosal pattern was obliterated. Exploratory laparotomy was halted at the very last moment by the hitherto unexpected radiographic findings. Subsequently the patient developed a phlyctenular conjunctivitis which with the erythema nodosum characterizes this disease. Under sulfasuxidine and sulfaphthalidine oral therapy, fever has disappeared and abdominal pain has ceased except for occasional slight periodic recurrences.

Many instances of this type of fever due to ileo-jejunitis have been encountered. It is of interest to note the interval between the onset of the fever and the eventual recognition of the cause. This is largely so because the diarrhea is usually so slight, although abdominal pain is commonly present and should be significant. If diarrhea is present the cases are occasionally mistaken for sprue, although the existence of fever should readily differentiate the two diseases. The most common mistake is to accept brucellosis as a working diagnosis.

In our early experience with ileitis we encountered a case of continuous fever of long duration (some years), which because of a positive agglutination test for brucella although in low titer was reported [4] as one of continuous fever due to brucellosis with the "unusual feature of unexplained roentgenographic changes in the distal ileum." After the appearance of the first publication upon regional ileitis, the original physician recognized the true origin of the fever and the real nature of the case, and the diagnosis of terminal ileitis was confirmed at operation.

Differential Diagnosis: In general, these cases of low-grade continuous fevers with minimal diarrhea and abdominal pain, particularly when complicated by ocular manifestations, articular involvement or by erythema nodosum, are overlooked because they so closely resemble rheumatic fever, subacute bacterial endocarditis, lupus erythematosus disseminatus (Libman-Sachs disease) or brucellosis. The occasional presence of slight eosinophilia makes the suggestion of periarteritis nodosa all the more likely. The not infrequently associated chronic valvular disease of the heart, plus the articular involvement and the erythema nodosum constitute a syndrome which simulates rheumatic fever very closely. If in addition, as in one case, one observes the onset of an acute endocarditis, with a systolic murmur of daily increasing intensity and high fluctuating temperatures, with negative blood cultures, the similarity to acute rheumatic fever is most startling. The rapid subsidence under penicillin and sulfasuxidine and the eventual cure of the condition by ileo-transverse colostomy, short-circuiting the diseased terminal ileum and ascending colon, removed any doubts as to the origin of the fever, the endocarditis and the articular manifestations. Only by the most careful clinical observations and laboratory tests can these cases of continuous fever of intestinal origin be differentiated from Hodgkin's disease, from subacute bacterial endocarditis, from diffuse lupus erythematosus without the characteristic facial rash. The diagnosis rests upon the proper evaluation of the abdominal symptoms of pain, cramps and diarrhea, no matter how slight, and the utilization of roentgenography for the eventual recognition of the causal pathological factor.

Needless to say, the fluoroscopy and the reading of the roentgenograms must be undertaken by an expert in this field, and adequate time and patience should be devoted to studying the hourly films if they should be indicated because of the nature of the case.

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IS THERE AN INTRINSIC ASTHMA?*

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THE classification of patients with bronchial asthma into two groups, namely, extrinsic and intrinsic, was first advocated by Walker [1] in 1918. When the patients exhibited positive skin reactions, the disease was supposedly associated with external causative agents; in patients with negative reactions, so-called intrinsic causes, especially sensitivity to bacteria, were held responsible. Rackemann [2] reported in 1927 that among 1,074 asthmatic patients there were an equal number of extrinsic and intrinsic cases. These investigators did not enlarge upon the clinical manifestations or pathological lesions in order to substantiate their classification which is accepted by most authorities. Since less reliance is now being placed on skin tests, the number of patients termed intrinsically asthmatic has decreased. Nevertheless, there are few textbooks, medical meetings, case reports upon asthma, or patients' hospital records in which emphasis is not placed on this distinction.

Cohen [3] has recently lent his support to this classification. In fact, he has attempted to establish the clinical syndrome of "intrinsic asthma" by setting down the following criteria: "Characteristically intrinsic asthma begins at about 40 years of age with a dry, spasmodic cough," gradually developing into wheezing. "Nasal symptoms are much less common than in cases of extrinsic asthma, although nasal and sinus polyposis are common findings. Skin tests with common allergens are uniformly negative. Environmental control in filtered air is not followed by complete relief from symptoms. Many intrinsic asthmatics are allergic to drugs such as acetyl salicylic acid." Cohen emphasizes the constancy of the attacks and the tendency to permanent tissue changes namely, emphysema, cylindrical bronchiectasis, hyperplastic sinusitis, nasal polyposis and periarteritis nodosa. He notes a high blood eosinophilia and the fact that this syndrome is responsible for the high death rate in asthmatic patients over 40 years of age.

An analysis of this description does not reveal any apparent difference from "extrinsic" asthma with the exception perhaps that the skin tests are "uniformly" negative and that the onset of the condition occurs at about 40 years of age. The description is otherwise typical of true allergic asthma regardless of its cause. There is no apparent reason why patients with nasal and sinus polyposis are relatively free from nasal symptoms, nor is it clear why bronchial asthma which is aggravated or caused by drugs should be termed "intrinsic." No pathological basis for this syndrome is offered nor are there any typical cases recorded in the literature. The concept is weak-

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ened by the introduction of a third group, namely "combined extrinsic and intrinsic asthma," of which Cohen distinguishes two sub-groups, namely "the primary intrinsic with extrinsic complications," and vice versa.

The most significant point brought out by Cohen, however, is the utter hopelessness with which he views the existence of intrinsic asthma. He speaks of the "waste of the physician's time and the patient's money" if intrinsic asthma is not recognized. Such a conception is actually shared by many, perhaps by most, leading allergists. It cannot fail to have serious consequences. Indeed, I have seen patients in whom treatment has been abandoned because their asthma was defined by the physician as "intrinsic." Such an attitude by the physician necessarily creates a great deal of despondency in the patient.

A thorough investigation on this subject is indicated because the concept of the term intrinsic asthma is so deeply rooted in the minds of most clinicians that it interferes with effective treatment. The following questions will be taken up:

1. Is intrinsic asthma a clinical syndrome?
2. Are there exclusively intrinsic or extrinsic causative agents which justify the uses of the terms intrinsic or extrinsic?

Before discussing these questions, brief reference should be made to the establishment of the diagnosis of asthma. In diseases other than asthma in which the causes are difficult to identify, such terms as "idiopathic" or "intrinsic" have been utilized. It is indeed tempting to apply such a term to those cases of asthma in which skin tests do not yield satisfactory data and in which the course appears at present to be hopeless. Three groups of diseases are encountered in which diagnostic problems arise and to which the term intrinsic may wrongly be applied: The first column of table 1 lists the conditions simulating allergic asthma out of a total of 1,442 patients with asthma. Some had been referred with the diagnosis "asthma," while others had actually been treated in my office for some time for "asthma" until further observation resulted in the proper diagnosis. The failure to respond to allergic management in patients who do not exhibit satisfactory skin tests should suggest the possibility of a faulty diagnosis. The second column of this table presents some of the unusual complications of allergic asthma, the presence of which may account for diagnostic and therapeutic difficulties and thus suggest the diagnosis of intrinsic asthma. The third column records true allergic asthma as combined with other conditions which may tend to induce wheezing and which might make asthma appear intrinsic. Probably the most impressive case is that of a 36-year old woman, Mrs. W. N. (case 5) with typical allergic asthma and completely negative roentgen-ray findings who failed to improve until a paralysis of both vocal cords due to injury of the recurrent nerves from a former thyroid operation was properly diagnosed and surgically corrected.

TABLE I

Conditions Encountered of "Wheezing—that is not asthma" in 1,442 Cases

1. Non-allergic wheezing simulating allergic asthma		2. Complications of allergic asthma		3. Conditions coincident with allergic asthma	
Chronic bronchitis	18	Permanent bronchiectasis	7	Active tuberculosis	2
Tuberculosis	12	Chronic pneumonitis	3	Paralysis of both recurrent nerves	1
Pulmonary carcinoma	5	Loeffler's syndrome	3	Substernal goiter	1
Cardiac decompensation	4	Cystic degeneration of lungs	2	Pulmonary syphilis	1
Aortitis	3	Spontaneous pneumothorax	1	Benign tumor in hilar region	1
Cystic lungs	3	Atelectasis of one lobe	1		
Monilia infection	3				
Pneumoconiosis	2				
Spontaneous peumothorax	2				
Goiter	2				
Foreign body in bronchi	2				
Pancoast tumor	1				
Esophageal stricture	1				
Pulmonary abscess	1				
Total	59		10		6

I. SYNDROME OF INTRINSIC ASTHMA

In order to determine whether or not there is a syndrome of intrinsic asthma, a search of our records was made for patients whose signs or symptoms would fulfill all or some of the criteria of this syndrome. From a total of 1,442 asthmatic patients seen from 1942 to 1945, 323 cases were selected because they had chronic, perennial asthma and had been observed sufficiently long to permit proper evaluation of their disease.

1. *Age of Onset:* Since the age of onset was thought to be a determining diagnostic feature, the 323 patients were grouped into four categories (table 2). No noticeable difference was observed in the various age groups in the severity and chronicity of the attacks or with respect to the development of complications. Considering, however, the ages at which they were first seen, it was striking that infants and young children manifested by far the most severe symptoms. The attacks were associated with considerable shock and often followed by pneumonitis. They responded least to the ad-

ministration of epinephrine and aminophyllin, while Benadryl was of greater value in these patients than in the older individuals. Because of the febrile course from the penumonitis and because skin reactions were often negative at this stage, these conditions may be regarded as being of bacterial origin and thus be termed intrinsic. However, previous observations [4] indicate that such attacks were actually due to the common allergens. As these

TABLE II

The Skin Reactivity and the Results of Treatment in Relation to the Ages for 323 Chronic Asthmatic Patients

Age of onset	Total	Skin reactivity			Results					
		Very strong	Positive	Doubtful and negative	Well	Improved	Stationary	Worse	Died	Data insufficient
0–20	158	11 (7%)	113 (72%)	34 (21%)	20 (13%)	102 (64%)	15 (9%)	2	1	18
21–40	87	5 (6%)	63 (72%)	19 (22%)	7 (8%)	58 (67%)	10 (11%)	1	–	12 (13%)
41–60	74	6 (8%)	50 (68%)	18 (24%)	4 (6%)	41 (55%)	14 (18%)	3	4	8 (10%)
61–80	4	—	3	1	—	2	—	1	–	1
Total	323	22 (7%)	229 (70%)	72 (23%)	31 (9%)	203 (63%)	39 (12%)	7 (2.3%)	5 (1.7%)	39 (12%)

children grew older, the febrile and "infectious" character gave way to the usual picture of allergic asthma, in most instances assuming a seasonal aspect and becoming much less severe and frequent.

2. *Negative Skin Tests:* Among the 323 cases, 22 (7 per cent) gave very strongly positive skin reactions; 229 (70 per cent) definitely positive; and 72 (23 per cent) reacted doubtful and negative to intracutaneous skin tests. According to table 2, the skin reactivity is approximately constant in the various age groups. It was generally observed that patients exhibiting strong reactions responded to treatment more readily than others; yet, several individuals with minor positive and questionable reactions, improved considerably when the results of these doubtful tests were made the basis for the allergic treatment. Table 2 demonstrates that there were very few of the 323 patients who fulfilled all three criteria of intrinsic asthma discussed so far, namely: constant attacks, onset at about 40, and negative skin reactivity.

3. *Complications:* An effort was made to determine whether or not the syndrome of intrinsic asthma could be detected more readily among those individuals whose asthma was complicated by secondary changes than in those without complications. It is difficult to present statistical evidence on this point. The three most common complications of allergic asthma, bronchiectasis, sinus infection and pneumonitis, often occur at the height of an asthmatic attack and disappear after its subsidence, during a time when the patient is being treated by his physician rather than studied by an allergist. In bronchiectasis, with the use of penicillin and the employment of frequent bronchoscopic aspirations in conjunction with allergic manage-

ment, improvement usually follows provided that the lesions are due to allergic causes and are not too far advanced. Seven patients had what appeared to be chronic bronchiectasis, three of whom died. In all seven, in addition to the presence of chronic infection, extrinsic causes were demonstrable by skin tests.

Practically every patient manifested some degree of sinus disease at some time. Indeed, the persistent absence of sinus involvement should make one question the diagnosis "allergic asthma." The extent of polypoid degeneration of the nasal membranes and the presence of secondary infection varied with seasonal influences and with the effectiveness of the treatment. In five rather advanced cases of asthma, such extensive changes were present that surgical treatment was necessary, and was followed by improvement of the asthma. When sinus infection dominates the clinical picture, the classification "intrinsic asthma" is particularly suggestive. However, in these five cases, there was sufficient evidence to prove that the infection was superimposed upon allergic changes.

In 12 of 19 asthmatic patients with heart disease, the cardiac history antedated the onset of asthma. In only two of the seven remaining patients an etiological relationship of the heart disease with the asthma appeared possible. Their asthma was proved to be due to extrinsic causes. Incidentally, Mrs. W. H. (case 68), the patient whose asthma had been of the longest duration (65 years) showed no evidence of heart disease. In the other, less common, complications listed in table 1, column 2, asthma on the basis of allergy was definitely established and skin tests were positive. Every one of these individuals was afflicted with extremely severe and chronic asthma, yet treatment benefited even the patients with such "intractable" conditions as the two individuals with cystic degeneration of the lungs.

4. *Refractoriness to Treatment:* Since this constitutes another criterion of the syndrome of intrinsic asthma, an analysis of those patients whose condition deteriorated or who died may yield further information.

Before presenting this analysis, it is necessary to dwell briefly on a few essential points concerning the treatment which differs to some extent from that generally employed. In my experience, chronic perennial asthma consists of a series of acute exacerbations. These usually coincide in summer with the peaks of the three pollen seasons; in winter with the prevalence of bacterial infections, with the prevalence of fungi in the air, and, with the beginning of the heating of homes (house dust!). Treatment is therefore primarily directed toward hyposensitization on a perennial basis against these principal antigens, while diet and other eliminative measures play a secondary part except where there are clear-cut indications for their use. When infections are prevalent, use is made of penicillin and sometimes of sulfonamides. In practically all chronic cases, we avail ourselves of the great benefits derived from repeated blood transfusions and from what is probably the most effective measure, repeated bronchoscopic aspirations of mucus, as outlined elsewhere.[5]

Table 2 reveals seven patients whose disease was progressive and five additional ones who died. In four of the seven cases (cases 8, 39, 40, 56), the diagnosis of allergic asthma might be questioned. There was evidence on roentgen-ray of chronic inflammatory processes in the lungs, which in two cases (cases 8 and 56) represented foci of healed tuberculosis; in the two others, chronic pneumonitis was present in the lower portions of the lungs. These conditions may or may not have been the source of their wheezing. The remaining three cases were the only ones encountered to which one might possibly apply the term "intrinsic asthma." In spite of the most thorough clinical observations no clues as to the cause of the disease were detected:

Mr. J. T. (case 279), 34 years of age, had had chronic wheezing and cough which began shortly after birth and was more pronounced during the winter months. This condition began to be much more severe at the age of 32. Since then the attacks had occurred daily. The patient had otherwise been in excellent health. There were no febrile episodes at any time nor were there any symptoms referable to nasal involvement. There was a family background of asthma: no sensitivity to any antigen was detected by the history. The physical examination, roentgen-ray investigations of the chest and sinuses, including lipiodol studies of the lungs, bronchoscopic examination and laboratory studies revealed no unusual findings other than slight emphysema, the characteristic asthmatic wheezing throughout the lungs and some thickening of the mucous membranes of the sinuses. The intracutaneous skin tests were negative. During the two year period while the patient was under observation, this condition was resistant to every type of treatment employed. He recently moved to California for "a change in climate" from where he reported no improvement.

Mr. K. W. (case 235), aged 35, developed attacks of asthma of a rather unusual pattern at the age of 22. In addition to occasional wheezing in the morning and upon exertion, severe seizures occurred two to three times a year. They were always preceded by what appeared to be an upper respiratory infection with marked rhinorrhea and the production of very large amounts of watery sputum. At the height of the attacks, extreme shock, fever and leukocytosis were present. During these attacks, the chest findings showed characteristic evidence of bronchial asthma, but neither epinephrin, aminophyllin, nor Benadryl was of any avail. Sulfonamide drugs and penicillin, which were administered because of the fever, were of no benefit. The patient, who has been under my observation for 12 years, had been free from attacks during a period of three years after he had received several blood transfusions (Waldbott [5]). Subsequently, however, the attacks recurred.

Miss M. W. (case 286), aged 29, had asthmatic attacks which came on gradually at the age of 19. They usually occurred at night and often required injections of epinephrin (0.1 to 0.2 c.c.). There was no family background of allergy nor was there a history of sensitization to foods, animals, etc. In addition to the findings of bronchial asthma in the lungs, the patient was considerably underweight. The chest findings were those encountered in uncomplicated bronchial asthma. The patient has coöperated fully for four years. She has been subjected to repeated laboratory and roentgen-ray studies and rhinological and bronchoscopic investigations which revealed nothing unusual. There has been no effect on the course of the disease from all the therapeutic measures employed other than a five-day period of complete freedom from attacks following injections of milk and a similar period after the administration of large doses of iodides and stramonium. Interestingly enough, during the

past year she exhibited rather strong reactions on intradermal skin testing, whereas these tests had been entirely negative on three previous occasions when carried out with the same technic.*

There is no question but that these patients present serious problems, both for diagnosis and treatment. In some, there may have been pathological changes other than those due to allergy. In the others, the clinical picture varies so greatly in each case that it is impossible to group them into a single clinical entity. There are certainly no common denominators with respect to age of onset, skin reactivity, or progress. This point is further elucidated by an analysis of the fatalities.

5. *Fatalities:* All five patients who died had been clinically sensitive to extrinsic substances and had given strongly positive skin reactions.

Three presented bronchiectasis, which was associated in one case, Mr. J. McC., aged 60 (case 320), with advanced cardiac damage. Another of the three, Mr. W. F., aged 52 (case 261), had for several months improved considerably, having especially benefited from penicillin and repeated bronchoscopic aspirations. He died very suddenly during a coughing spell at night in a manner suggesting that mucus might have obstructed one of the main bronchi.† The autopsy showed some bronchiectasis. The fourth fatality was Mrs. J. L., aged 42 (case 196) with the diagnosis thrombo-angiitis obliterans manifesting hypertension, chronic nephritis and diabetes. Although her skin tests had been markedly positive, she had never shown improvement from any treatment during the five years she had been under observation.

Miss D. W., aged 16 (case 221), is of special interest because intrinsic causes must have been primarily responsible for the asthma although the clinical picture varied greatly from the above described syndrome. Her first attack coincided with the first menses at the age of thirteen. Since then, very acute and severe seizures occurred regularly every four weeks, always two to three days before the menses, subsiding within three days. During the past year, the attacks became more prolonged, gradually extending throughout the period of the menses, but varying in intensity according to the original pattern. They became so severe that the patient had to be admitted to the hospital 10 times during one year's period. On each occasion she was unconscious and in severe shock. Bronchoscopic aspirations were resorted to each time as a life-saving procedure. She always recovered promptly immediately after bronchial aspiration of large amounts of tenacious material. When, in September 1943, on a day of high ragweed count, during such an attack, the bronchoscopist was not available immediately on admission to the hospital, she died.

Physically, this patient presented the usual findings of marked emphysema and typical wheezing. There were no secondary changes such as bronchiectasis or pneumonitis. The electrocardiographic and roentgen-ray studies showed the heart and lungs to be normal except for the presence of emphysema. The esosinophile count ranged from 4 to 12 per cent. Skin testing revealed many moderately severe reactions to such extrinsic sources as foods, ragweeds and other inhalants. An attempt to hyposensitize her against some of these antigens, as well as diets and other eliminative procedures, did not produce any improvement whatsoever. Intracutaneous skin tests with anterior pituitary extract, theelin and progesteron produced flares, but no typical wheal. Injections of progesteron, which have been helpful in the treatment of similar cases with premenstrual asthma, gave no relief.

* Addendum (May 17, 1947): Since August 1946 after being placed on a high caloric diet disregarding all positive foods, this patient has been practically free from asthma.

† *Note:* This is considered the most common mode of death in asthma.

II. "Intrinsic" Causes

Disregarding the symptom complex of intrinsic asthma, some have applied the term "intrinsic" when the asthma is believed to be exclusively or at least primarily due to causes arising from within the organism. In the following review of the various factors involved, it will become apparent that skin tests cannot be reliably employed for any of these intrinsic sources.

Cold Sensitivity: Most of the 323 patients displayed "sensitivity" to sudden changes in temperature, especially to cold. Exposure of their skin to cold temperature and, more frequently, inhalation of cold air, induced wheezing. In 21 cases, a history was obtained that ingestion of ice cold drinks had this effect. The literature discloses evidence that the production of histamine is stimulated by sudden application of cold. However, merely the physical stimulus of inhaled cold air may produce an attack, through irritation of the mucous membranes of the nose and bronchi. In none of our cases could the asthma be attributed exclusively to sensitivity to cold.

Infection: Bacterial infection may account for asthmatic seizures. On the other hand, the presence of pus and bacteria in the upper air passages or the sinuses does not necessarily indicate a primary infection. Cohen, Kline and Rudolph [6] observed that an allergic wheal may become indistinguishable from an inflammatory process after three hours. By the same token, a process manifesting all the earmarks of an infection in the sinuses, in the bronchial tree and even in the lungs, may be entirely due to allergy. In some of the cases of this series, allergic pneumonitis had been wrongly diagnosed "virus pneumonia" because no specific organism could be demonstrated as their excitant. True infections were present at some time or another in practically every case of our series. Asthmatic seizures induced in this manner usually improved with the aid of sulfonamides and penicillin. During the height of an acute infection, the skin reactivity to the common antigens often decreases in intensity or completely disappears.

Endocrine Products: Among the 148 women at the menstrual age and above, 47 gave a history of having had an aggravation of their symptoms before the menstrual period. This relatively high incidence corroborates a similar observation by Waldbott and Bailey [7] showing that 22 out of 125 patients with various allergic diseases exhibited this tendency. In the blood of these cases with premenstrual aggravation, a deficiency of estrogenic substance was demonstrated. In contrast with the observation of Zondek,[8] skin reactions with extracts of estrogenic substances were inconclusive upon intracutaneous testing.

Psychogenic Factors: In a disease as disabling and chronic as bronchial asthma, it is to be expected that many patients should develop certain mental complexes which tend to enhance their symptoms. The exaggerated attention given to the patient by their attendants, especially by parents, the many don'ts in the life of an asthmatic, the habitual use of certain drugs, the disruption of family life and marriage relationship as the result of attacks, finally

the fear of strangulation during an attack, are factors which may induce such complexes. There were, indeed, many patients in whom attacks could be precipitated by mental influences and controlled by the administration of placebos. This mode of origin was not found to be a dominant factor on careful analysis of each individual case.

Other Possible Sources: Among intrinsic agents, Urbach [9] discusses products resulting from parasites within the body, from digestion in the intestinal tract, certain physiological fluids such as insulin, colostrum and mother's milk. Most of these factors are of speculative interest only and it could not be ascertained in our cases whether or not they played a part.

Summary

1. Asthma has been classified as extrinsic and intrinsic according to whether causative agents are demonstrable which enter the system from without or arise within the organism. In addition, some have described a syndrome of intrinsic asthma characterized by such clinical features as age of onset at 40 or above, negative skin reactions, progressive course and intractability to therapy.

2. In order to determine whether or not such a syndrome exists and whether a distinction between extrinsic and intrinsic asthma should be made on the above basis, 323 individuals were selected from a total of 1,442 asthmatic patients. They had perennial, continuous wheezing and had been under observation sufficiently long to permit a proper evaluation of their conditions. Among those excluded were cases with asthmatic wheezing which might easily have been interpreted as allergic asthma of the "intrinsic" type.

3. In seven of the 323 patients, the disease progressed and five additional ones died. In none of these could the above described syndrome be identified. In three cases, no clues as to the origin of the attacks could be detected. In each one the pattern of the attacks appeared different and it is impossible to group them under the common heading of "intrinsic asthma."

4. Intrinsic causes were definitely responsible for attacks in a large number of the 323 patients. Among these the most important ones were sensitivity to cold temperature, to endocrine products (premenstrual aggravation!) and bacterial infections. Psychogenic factors, products of digestion, or such physiological fluids as insulin, liver extract, colostrum may or may not play a part. In no case were such intrinsic factors found to be the only causes to the exclusion of those termed extrinsic.

5. This evidence indicates that there is no justification for the diagnosis of intrinsic asthma as a symptom complex and that the concept of such a syndrome may lead to faulty diagnosis and to abandonment of treatment at a time when treatment is needed and may be most effective. The term "intrinsic asthma" based on the assumption that the disease is due to intrinsic causes is misleading since such causes are not present to the total exclusion of extrinsic causes.

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DISSECTING ANEURYSM OF THE AORTA: A PRESENTATION OF FIFTEEN CASES AND A REVIEW OF THE RECENT LITERATURE *

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DISSECTING aneurysm of the aorta was first described by Nicholls [1] in 1761. Laennec [2] in 1819 was the first to employ the term dissecting aneurysm and Swaine [3] in 1856 was the first to make a correct ante-mortem diagnosis. In 1863 Peacock [4] published his review of 80 cases and in 1933 Shennan [5] published his monograph of 300 cases, to which he added 17 of his own. Since then there have been many excellent descriptions of the various aspects of this disease, among them being the reports of Logue,[6] Schnitker and Bayer,[7] Peery,[8] Weiss,[9] and Sailer.[10]

Although dissecting aneurysm is not a common occurrence, it is of importance to the clinician because of the variable symptomatology that it may produce. Despite the fact that dissecting aneurysms have been recognized by pathologists for many years, it is only recently that clinicians have regarded it as more than a medical curiosity. In Shennan's [5] series of 317 cases, the diagnosis had been made in only seven. In 1942 Flaxman [11] reviewed 112 cases reported since 1933 and found that the correct ante-mortem diagnosis had been made in 25. Thus, of 431 reported cases, the diagnosis had been made in 32 (7.9 per cent).[11] Recently clinicians have become better acquainted with the symptomatology so that the diagnosis is made in 10 to 30 per cent of the cases. In this series the correct ante-mortem diagnosis was made in six of 15 cases (40 per cent).

The true incidence of dissecting aneurysm is not known but the autopsy incidence has been reported by various investigators as follows: .14 per cent (Flaxman [11]); .18 per cent (Peery [8]); .5 per cent (Weiss [12]); .7 per cent (Logue [6]); .22 per cent (Sailer [10]); and .4 per cent (Ritvo and Votta [13]). Mote and Carr [14] in a review of the statistics of the Coroner's Office in San Francisco found that dissecting aneurysm is the cause of 1.1 per cent of all cases of sudden death (after exclusion of death due to violence).

In this series 11 cases were in males and four were in females. This corresponds to the figures reported by McGeachy and Paullin [15] (74 per cent in males) and Glendy et al.[16] (11 of 13 were males).

The ages of our patients varied from 35 to 87 years. There were three cases between 31 and 40; one between 41 and 50; six cases between 51 and 60; three cases between 61 and 70; one case 75, and one case 87. It is interesting to note that in the cases that occurred in patients over 50 years of age, the ratio of males to females approaches 1 : 1 (6 males in 10 cases over 50); this was observed by Shennan.[5] Most cases of dissecting aneurysm

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TABLE I

Case No.	Age	Sex	Color	Exertion Prior to Onset	Admitting Diagnosis	Final Diagnosis
1	38	Male	Colored	None	Dissecting aneurysm	Dissecting aneurysm of thoracic aorta
2	67	Male	Colored	None noted	Cerebro-vascular accident	Dissecting aneurysm of entire aorta
3	57	Female	White	None noted	Dissecting aneurysm of abdominal aorta	Incomplete rupture of the aorta
4	54	Male	White	None noted	Coronary occlusion	Dissecting aneurysm of entire aorta
5	75	Male	Colored	None noted	Pneumonia with poss. coronary occlusion	Dissecting aneurysm of thoracic aorta
6	40	Male	Colored	None noted	Dissecting aneurysm	Dissecting aneurysm of thoracic aorta
7	54	Male	Colored	None noted	Dissecting aneurysm	Dissecting aneurysm of arch of aorta
8	60	Female	Colored	None noted	Coronary occlusion	Dissecting aneurysm of abdominal and thoracic aorta
9	87	Female	White	None noted	Partial intestinal obstruction	Dissecting aneurysm of superior mesenteric artery
10	62	Male	White	None noted	Coronary occlusion	Dissecting aneurysm of thoracic aorta
11	46	Male	Colored	None noted	Luetic heart disease	Dissecting aneurysm of thoracic aorta
12	63	Male	White	During an argument	Coronary occlusion	Dissecting aneurysm of ascending aorta
13	60	Male	White	Driving to work	Dissecting aneurysm	Dissecting aneurysm of entire aorta with dissection of left common carotid artery
14	35	Male	White	At work at a desk	"La grippe"	Dissecting aneurysm of aorta
15	60	Female	White	At home doing housework	Dissecting aneurysm	Dissecting aneurysm

occur in patients between 40 and 70 years of age.[17, 6, 18] In Crowell's[19] series 80 per cent of the patients were over 40; 12 of Glendy's[16] 13 cases were in patients over 40, and 12 of our 15 were over 40. Schnitker,[7] however, in a review of 560 cases found 141 (25 per cent) cases in patients under 40 years of age. The youngest case was recorded by Frei[20] (14 months old) and the oldest was recorded by Shennan[5] as being nearly 100 years old.

The etiology of dissecting aneurysm is not clearly understood; but there are several factors which are believed to play a part. Certain of these are discussed below.

The relationship of trauma and exertion to the formation of a dissecting aneurysm is still disputed but most investigators [7, 14, 21] believe that it is purely coincidental. Weiss [9] stated that he believed that most of the cases reported following trauma are not instances of true dissecting aneurysm. Glendy et al.[16] found that 40 per cent of their cases occurred after mild exertion (two while stooping; one during the act of vomiting; one during intercourse; one while arguing a case in court). In a review of 127 cases McGeachy and Paullin [15] found a history of exertion at the time of onset in 33. In only two of our cases could we find any relation to exertion; one during an argument and the other incident to housework.

It was formerly believed [17, 18, 6, 22] that hypertension was of prime importance to the formation of a dissecting aneurysm, but recent investigators believe that hypertension is of secondary importance.[7, 14] The incidence of hypertension in cases of dissecting aneurysm has been recorded by various authors as follows: McGeachy and Paullin [15] (60 of 127 cases); Glendy, Castleman and White [16] (8 of 11 cases); Hamburger and Ferris [23] (1 of 6 cases); Shennan [5] (131 of 163 cases); Thomas and Garber [18] (107 of 151 cases). Ten of our 15 patients (67 per cent) had either a history of hypertension or elevated blood pressures on admission (table 3). Of the 560 cases reviewed by Schnitker [7] 80 per cent were found to be hypertensive, but in the 141 cases under the age of 40 only 50 per cent were hypertensive. Oppenheim [24] demonstrated that it takes a pressure of two to three thousand millimeters of mercury to rupture the aortae of fresh cadavers. In view of the above discussion it may be concluded that: (1) although hypertension is usually present, its absence does not exclude the possibility of a dissecting aneurysm; (2) it is doubtful if "increases of pressure alone could reach sufficient magnitude in human subjects to cause actual dissection of the aorta" [10]; (3) hypertension will be found in 70 to 80 per cent of the patients over 40 years of age, whereas only 50 per cent or fewer of patients under 40 years of age will be found to be hypertensive.[7]

Formerly syphilis was believed to be an important predisposing factor, but recent investigations show that it is of minor importance. Syphilis has been found in many cases of dissecting aneurysm, but this is believed to be coincidental. Thus, in a review of 141 cases Schnitker and Bayer [7] found only five cases of syphilis; Shennan [5] and Mote and Carr [14] found evidence of syphilis in 10 per cent and 18 per cent of their cases respectively; McGeachy and Paullin [15] found six cases of syphilis in a review of 127 cases of dissecting aneurysm, and in two of our 15 cases (table 4) there was either serological or pathological evidence of syphilis. In case 5 there was a luetic saccular aneurysm and luetic aortitis beyond the intimal tear which were not involved in the dissection. In case 11 the dissection progressed

through the area of syphilitic aortitis. Weiss [9] and Sailer [10] point out that in syphilis the pathological process tends to fuse the various layers of the aorta thereby hindering dissection. Weiss [9] also presents a case in which the dissecting aneurysm extended up to, but did not involve the syphilitic area.

In the cases occurring in patients under the age of 40 there seems to be a distinct relationship between pregnancy and congenital anomalies of the aorta, and dissecting aneurysms. Schnitker and Bayer,[7] in their excellent review of this subject, found 141 cases out of a total of 560 (25 per cent) to have occurred in patients under 40 years of age. Of this group 49 (approximately 35 per cent) were in females and 24 (49 per cent) of these were pregnant. In only two of these did dissection occur in association with labor (two were post-partum and 20 were ante-partum) so the dissection cannot be attributed to the strain and blood pressure changes occurring during labor. McGeachy and Paullin [15] report 26 cases in females, six of whom were pregnant. Kinney, Sylvester and Levine [25] have recently reported a case of coarctation and acute dissection of the aorta in a pregnant patient which was diagnosed ante-mortem. Whether a true cause and effect relationship exists between pregnancy and dissecting aneurysm is not known, but it may be due to the hormonal changes which occur in pregnancy which may, in some way, weaken the aortic wall so that it is more susceptible to dissection.

Another predisposing factor is the presence of a congenital anomaly of the aorta, especially coarctation. Hamilton and Abbott,[26] in a review of 200 cases of coarctation of the aorta, found that 33 (16.5 per cent) of these died of a dissecting aneurysm. Schnitker [7] found that 45 of his 141 cases in patients under 40 years of age had either a true coarctation or distinct narrowing of the aorta. The case reported by Kinney, Sylvester and Levine [25] had a true coarctation of the aorta. The explanation of the occurrence of dissecting aneurysms in coarctation of the aorta is that in coarctation there is a primary deficiency of the media with a resultant weakened wall so that dissection may occur more readily than in a normal aorta. None of our 15 patients were pregnant and in no case was there any evidence of coarctation or of other congenital anomalies of the aorta.

Probably the most important factor in the formation of dissecting aneurysm is disease or weakening of the vessel,[14, 15, 10] especially of the medial coat. The nature of this deficiency or disease is not definitely known. Some observers [27, 28] believe it is the "medionecrosis aortae idiopathica cystica" as described by Erdheim. Schattenberg and Ziskind [29] present two cases of dissecting aneurysm and in both the medionecrosis as described by Erdheim was present. Glendy, Castleman, and White [16] found it in six of their 13 cases. We were unable to find it in any of our 15 cases and Rottino [30] was unable to find it in any of his 12 cases. Holland and Bayley [28] found 27 cases of medionecrosis aortae idiopathica cystica reported in the

literature, all of whom died of the effects of a dissecting aneurysm. Sailer [10] and Rottino [30] have reviewed the medial changes which occur in dissecting aneurysm and both have described several different types of degenerative changes which occur in the media and for a description of these changes the reader is referred to the original articles. From the above discussion it can be concluded that medial change, the nature of which may be different in various cases, is of primary importance to the formation of a dissecting aneurysm. Whether the medial changes will be found to be similar to those described by Erdheim or of other nature is unknown, but it may be that if diligent studies of various sections of all aortae are carried out definite medial changes will be found in a great number of cases.

Atherosclerosis has been cited as playing a rôle in the formation of a dissecting aneurysm, but it by itself cannot be the sole cause for several reasons: first, atherosclerosis is least common in the ascending portion of the aorta and it is in this area that the great majority of intimal tears are located; second, the intimal tear usually occurs in the tissue between two atherosclerotic plaques and rarely through one. Shennan [5] found that in only six of 218 cases did the dissection begin at the base of an atheromatous ulcer.

It may be concluded that no single cause can be demonstrated as consistently producing the changes leading to a dissecting aneurysm.[10] Medial disease, the nature of which varies, and hypertension, with the systolic stretching and diastolic recoil seem to be the most important factors involved.

The pathogenesis of dissecting aneurysm although not definitely established, is believed to be as follows: as a result of the medial disease there is a rupture of the vasa vasorum with the formation of a medial hematoma, which splits the wall. This eventually ruptures through the intima (usual course) producing a rent in the intima through which the blood can force its way, thereby extending the dissection. The path of the dissection will vary with the location and extent of the medial lesion.[17, 6, 14, 31, 10] There are several cases on record in which no intimal tear could be demonstrated [6, 32, 23] and in this series of 15 there was one case (no. 8) in which no intimal tear could be found.

Peery [33] has recently reported a series of cases in which there are tears through the intima without true dissection. These he has labelled "incomplete rupture of the aorta" and believes that this may be a stage of dissecting aneurysm. We had one such case in our series (no. 3).

The intimal tear is usually located in the first few centimeters of the ascending aorta, but may occur anywhere. There is usually only one tear, but they may be multiple. The tear is usually elliptical or longitudinal and varies from 1 to 10 centimeters in length. The incidence of tears located in the ascending aorta, as given by various authors, is as follows: Schnitker and Bayer [7] (58 of 64 cases); Mote and Carr [14] (42 of 56 cases); McGeachy and Paullin [15] (42 of 79 cases); and Frei [20] (153 of 275 cases). McGeachy

TABLE II

Case No.	Location, Length and Direction of Tear	Extent of Dissection	Cause of Death	Degree of Atheromatosis	Other Findings
1	4 cm. below the arch of the aorta	Dissected down to the level of the diaphragm	Pneumonia	Moderate	
2	1 cm. elliptical tear 1½ cm. above the aortic valve. 2nd tear just above opening of right coronary artery	Down to the bifurcation of the aorta	Hemopericardium. Rupture through adventitia 8 cm. above aortic valve. 300 c.c. of blood in pericardial cavity	Severe	Extensive atheromatous degeneration of aorta
3	Numerous tears through the intima extending into the media	No true dissection	Coronary artery disease	Severe	Extensive atheromatous degeneration of aorta
4	1½ cm. above the aortic valve. Angular	Down to the bifurcation of the aorta	Hemopericardium. 350 c.c. blood in pericardial sac	Severe	Hemorrhage into tissue between pulmonary artery and aorta and into the musculature of the left atrium extending down to A-V line and covering area where S-A node and A-V bundle are
5	6 cm. jagged tear at beginning of the ascending aorta	Up and around the arch to just above the aortic cusps, and also into the innominate	Hemopericardium. 350 c.c. blood in the pericardial cavity	Moderate	Also showed a saccular (luetic) aneurysm and luetic aortitis beyond the location of the tear. An old healed myocardial infarction
6	1st tear 2 cm. in length and just above opening of right coronary and the 2nd tear 4 cm. in length and 1½ cm. above the first. These 2 communicated	To the level of the diaphragm	Hemopericardium. 250 c.c. blood in pericardial sac	Moderate	Tuberculosis of the left adrenal gland
7	1st tear a 1 cm. ragged vertical tear just above the left coronary ostia and the 2nd a 2 cm. transverse tear at the origin of the left subclavian	To the origin of the left subclavian artery	Cardiac dilatation and pulmonary edema	Moderate	Ruptured back into the lumen at the origin of the left subclavian artery

TABLE II—*Continued*

Case No.	Location, Length and Direction of Tear	Extent of Dissection	Cause of Death	Degree of Atheromatosis	Other Findings
8	No visible tears in the intima	From 7 cm. above to 7 cm. below the vertebral attachment of the diaphragm	Left pleural effusion. 500 c.c. bloody fluid in left pleural cavity	Marked	No tears in the intima or adventitia
9	Tear in the superior mesenteric artery, 2½ cm. from its origin	Extended up the superior mesenteric artery for 5½ cm.	Gangrene of the bowel with intestinal obstruction	Moderate	Thrombus occluded the artery and produced gangrene of the bowel
10	A rectangular tear 2 x 3½ cm. and 1½ cm. above the aortic valve on the posterior aspect of the aorta	To the level of the diaphragm	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	?	
11	1½ cm. in length and 2½ cm. above the aortic valve	To the level of the diaphragm	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	Severe	Tear through the adventitia on the anterior aspect of ascending aorta. Also luetic aortitis
12	A clean edged zigzagged tear 1 cm. above aortic valve on the right lateral aspect of aorta	Extended down over the atria, beneath the epicardium and up along the aorta to where it broke through the adventitia	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	Slight	
13	Transverse tear 1½ cm. in length, 2 cm. above the aortic valve	Extended down to a point 1 cm. above the bifurcation where there was a 2nd small transverse tear. Dissection extended up left common carotid and almost completely occluded the lumen	Hemopericardium. 200 c.c. fresh and clotted blood	Severe	No tear in adventitia. Thrombosis of right common iliac artery
14	2 cm. transverse tear at sinus of Valsalva	Down to the iliac artery	Hemopericardium	Moderate	Old healed dissecting aneurysm, beginning at ductus arteriosus
15	Just above the renal artery	Down into the right common iliac	Retroperitoneal hemorrhage	Marked	

and Paullin [15] found multiple tears present in 12 per cent of their cases, whereas Shennan [5] found multiple tears present in 11 per cent. In our series the location of the tears was as follows: Ascending aorta—10; descending aorta—two. In one case there was no tear present; in another the tear was in the superior mesenteric artery and in case no. 3 there were multiple tears

throughout the aorta. In four of our cases (27 per cent) more than one tear was present. "The localization of the greatest number of intimal tears in the supravalvular portion of the aorta appears to be due to the relative immobilization of the vessel at this point, together with the marked physiologic strain and pressure acting on this area." [34] Shattenberg and Ziskind [29] believe the reason for this localization of intimal tears is that it is in this portion of the aorta that medial degeneration most frequently occurs. It is probable that both of these factors play a rôle.

Once the dissection has begun it usually spreads centrifugally although occasionally it goes centripetally.[10] The dissection is limited to the ascending and transverse portions of the aorta in 30 per cent of the cases,[5, 15, 16] and extends to the abdominal aorta in 35 per cent. In about 15 per cent of the cases one will find a double-barreled aorta. In our series the dissection extended to the bifurcation of the aorta in four; to the level of the diaphragm in four; and to the arch of the aorta in three. In one case there was no true dissection (case no. 3); in another the dissection extended from 7 centimeters above, to 7 centimeters below the diaphragm (case no. 8); in one case the dissection involved the superior mesenteric artery (case no. 9); in one case there was a double-barreled aorta (case no. 14).

The dissection may take one of three courses: (1) progress and involve the entire aorta, and then rupture back into the lumen; (2) progress a variable distance and then cease (rare); (3) rupture through the adventitia into the pericardial, pleural, or abdominal cavities. This latter event is the most common result and occurs in 80 to 90 per cent of the cases and results in sudden death.[17] The incidence of external rupture is as follows: Frei,[20] 189 of 275 cases (73 per cent intrapericardially); McGeachy and Paullin,[15] 69 cases (74 per cent intrapericardially); Crowell,[19] 86 per cent of his cases; and Glendy,[16] 10 of 13 cases (31 per cent intrapericardially). Schnitker and Bayer [7] found rupture into the pericardium present in 78 per cent of their cases and in our series, rupture into the pericardium with cardiac tamponade was the cause of death in 67 per cent. Other sites of external rupture are the pleural cavities (more often the left) [9, 15]; mediastinum,[16] and abdominal cavities. Ten to 20 per cent of the patients will recover from the first acute attack, but half of these will develop a second dissecting aneurysm which may result in their death; the remainder, however, will recover and die of some other disease or accident. There are cases of healed dissecting aneurysm [5, 35, 36] on record in which the aneurysmal cavity became endothelialized and in some atherosclerosis developed.[35] Even if these patients recover from the dissecting aneurysm, many of them will die of congestive heart failure. Only one of our cases (case no. 14) had a healed dissecting aneurysm with endothelialization of the aneurysmal sac, but two and one half years later he had a second dissecting aneurysm which caused his death.

The diagnosis of dissecting aneurysm is dependent upon clinical awareness and acquaintance with the symptomatology and physical findings in

association with the location and direction of the dissection and the vessels affected. The symptoms most often found are:

Pain: This is the most striking symptom produced.[17, 6, 14, 31] It is usually sudden in onset, very excruciating, and often radiates to the back between the scapulae and into the neck. In some cases the pain radiates down the back and into the legs. The pain rarely radiates to the arms. The pain is usually precordial but may be substernal, epigastric, interscapular, or lumbar.[15, 16] In some the pain may begin in the legs. The pain is usually not relieved by ordinary doses of morphine. In our series of cases the location and radiation of the pain was as follows: In 10 cases the pain was above the diaphragm and in five it was below the diaphragm. In the cases in which the pain was above the diaphragm there were three cases in which it was substernal without radiation; two cases of substernal pain which radiated to back and epigastrium; two cases in which the pain was in the left lower

TABLE III

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
1	Recurrent attacks nausea for 3 days. Prior to admission severe pain in back and epigastrium which persisted	None	Not present. Hyperactive reflexes on the right	Hypertensive for several years, 230/130 on admission, 230/140 on day after admission, 230/135 on 2nd day, 200/100 on 3rd day	None noted
2	Severe substernal pain and unconsciousness until death	Mild	Patient unconscious	No history of hypertension. B.P. 132/86 on admission. No other notations	None noted
3	Severe "indescribable" intermittent epigastric pain for the past month, which radiated through to the back	No note	Not present	Hypertensive for past 5 years. B.P. 220/140 on admission. No other notations	None noted
4	Sudden onset of severe substernal tightness which lasted 5 minutes and was followed by collapse	No note	Not present	For past 1–2 years. Averaging 170/120. B.P. on admission 50/20, rose to 106/60; 140/110 (R.A.) and 120/100 (L.A.) next day	None noted
5	For 2 days prior to admission mild stabbing pains in his left lower chest which radiated to the right	None	Not present	Known hypertensive for 5 months. 180/120 on admission. Fell to 110/70 on the second day, and then gradually rose to 120/80 by the 5th day	None noted

TABLE III—*Continued*

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
6	Sudden onset of severe stabbing substernal pain which radiated to the back and epigastrium	Moderate	Not present	No history of hypertension. B.P. 215/110, rose to 270/140 2 hours later, then fell to 240/130 1½ hours before death	Loud aortic diastolic murmur, transmitted down left sternal border
7	Sudden severe pain in left lower chest	Moderate	Not present	No history of hypertension. 60/? on admission, 65/50 next day	None noted
8	Severe knife-like pain in R.L.Q. which radiated to back and left flank	Moderate	Not present	No history of hypertension. 113/84 on admission. 92/60 2nd day; 178/110 5th day; 120/90 14th day; 142/104 16th day; 114/80 20th day	No diastolic murmur noted. Loud systolic murmur at aortic area
9	Slight epigastric pain with nausea and vomiting for 3 weeks	None	Developed a right hemiplegia with hyperactive reflexes. Cleared up on 2nd day	No history of hypertension. 118/75 on admission. 120/65 next day	None noted
10	Sudden onset of substernal pain which radiated to epigastrium	Moderate	Developed a right hemiplegia with hyperactive reflexes 12 hours after admission	Known hypertensive for 3 yrs. (195/120). 150/120 on admission	None noted
11	Sudden onset of dyspnea and mild pains in region of heart. Went into shock, responded but died next day	Marked	Not present. Reflexes hyperactive	No history of hypertension. 180/90, both arms on admission. Dropped to 90/60 on 1/1/39 and rose to 115/70 on 1/2/39	Loud aortic diastolic murmur
12	Constricting pain in the suprasternal notch relieved by M.S. 7 hrs. later had sudden onset of severe nausea and vomiting, with mild epigastric pain. Relieved by M.S. Developed right hemiplegia 22 hrs. later and died in 1 hour	Marked	Hyperactive on right after developed hemiplegia	Hypotensive all of life. 75/56 when first seen, without any subsequent change	None noted
13	Sudden onset of severe pain in his throat. This was later replaced by substernal soreness and mild epigastric distress	Marked	No	No history of hypertension, 70/50 on admission. Rose to 130/70 that night; 145/90 next morning; 130/88 just prior to death	Faint aortic diastolic murmur at left sternal border

TABLE III—*Continued*

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
14	Sudden onset of severe substernal pain which persisted for 2 days. Continued to work. No pain for past 4 days but has had a "cold." Had been in hospital 2½ years previously with sudden onset of severe lumbar back pain. No cause found. Cleared with symptomatic treatment	No	No	B.P. 155/100–185/120 for past 2½ years; 200/115 on admission. No subsequent notations	High pitched aortic diastolic murmur
15	Sudden onset of severe abdominal pain which radiated down both legs and out to the right axilla. Very thirsty and dizzy. Pain persisted and vomited (no blood)	No	No	B.P. 180/90 to 230/130 for past 12 years. 96/86 on admission. Dropped to 84/80, 2 hours later	No notation of any murmurs

chest, and in one of these it radiated across to the right; one case of precordial pain without radiation; in one the pain originated in the suprasternal notch and radiated to the epigastrium and in the other the pain began in the throat and later was replaced by a substernal pain. In the five cases in which the pain began beneath the diaphragm it was epigastric on three occasions. In one there was no radiation; in the second the pain radiated to the legs and right axilla; and in the third it radiated through to the back. In one case the pain began in the back and radiated around to the epigastrium and in the other case the pain began in the right lower quadrant and radiated to the back and flank. In no case was there any pain in either arm. The pain was described as being choking, constricting, knife-like, stabbing or crampy. In all cases the pain was intense. There have been cases reported in which there was no pain present.[6, 24, 48]

Dyspnea: This is frequently observed, but is believed to be secondary to the pain. In some cases, however, the dyspnea will be caused by a hemothorax resulting from leakage from the dissecting aneurysm.[37] McGeachy and Paullin [15] found that 30 of 127 patients were dyspneic and Glendy [16] found dyspnea in eight of their nine cases. In our series there were five patients who were not dyspneic; three with marked dyspnea; three with moderate dyspnea and one with mild dyspnea; in two cases there was no notation as to dyspnea.

Syncope: This has been noted by some authors,[23] and was observed in one of our cases (case no. 4).

Hypertension: The rôle of hypertension has been discussed earlier but we would like to point out that although some patients with dissecting aneurysm are in shock when first seen [17, 7, 14, 23] one of the most common findings is an elevated blood pressure, which does not fall.[17, 16, 15, 7] Ten of our 15 patients had either a history of or elevated blood pressure when first seen. In our series the blood pressure rose on four occasions, made no change in three and fell in four. In four cases no subsequent blood pressures were recorded.

A second important physical finding is the sudden appearance of an aortic diastolic murmur,[17, 7, 38] with or without other signs of aortic insufficiency. This is a frequent finding since most of the intimal tears occur in the ascending aorta and as a result of the dissection there may be a distortion of the aortic ring so that there will be improper closure of the aortic valves.[7, 14] Glendy et al.[16] observed a diastolic murmur at the base (with a systolic murmur) in four of 10 cases; McGeachy and Paullin [15] observed a basal diastolic murmur in two and a to and fro murmur in 14 of 32 cases; Schnitker [7] found an aortic diastolic murmur in 24 per cent of 141 cases. In our series an aortic diastolic murmur was noted in four of 14 cases (29 per cent).

TABLE IV

Case No.	S.T.S.	X-ray Findings	Hbg.	R.B.C.	W.B.C.	Polys	Hematuria	Electrocardiogram
1	None	Enlarged heart. No mention of an enlarged aorta.	60%	3,350,000	12,000	72%	No	None taken
2	Negative	None taken	72%	3,850,000	9,800	78%	No urine report	None taken
3	None	None taken	81%	4,410,000	13,800	81%	No	None taken
4	None	None taken	75%	3,900,000	22,700	88%	No	Complete auricular ventricular dissociation
5	Positive	Saccular aneurysm of the arch of the aorta	72%	3,840,000	11,600	72%	No	None taken
6	None	Moderate degree of dilatation of the aorta. Heart at the upper limits of normal in size	88%	4,500,000	14,900	93%	No	None taken
7	Negative	Widening of the mediastinal shadow on the right. Enlarged heart	115%	5,810,000	21,400	81%	No	Deep depressed ST_2 and ST_3. Ventricular extrasystoles. T-waves upright

TABLE IV—*Continued*

Case No.	S.T.S.	X-ray Findings	Hbg.	R.B.C.	W.B.C.	Polys	Hematuria	Electrocardiogram
8	Negative	Marked enlargement of the heart to the right and left	65% (11/21) 53% (12/5)	3,690,000 3,030,000	15,700 10,200	89% (11/21) 75% (12/5)	No	Slurred QRS Lead III, inverted T_3. No other changes
9	None	No chest x-ray. Flat plate of abdomen showed dilated loop of bowel representing partial intestinal obstruction	90%	4,830,000	6,800	85%	No	None taken
10	None	None taken	None	None	26,000	83%	Few RBC in urine	All T-waves upright. Depressed ST_2 and ST_3. Elevated ST_4
11	Positive	None taken	94%	4,810,000	15,250	88%	Occ. RBC in urine	None taken
12	None	None taken	None	None	15,200	77%	No	None taken
13	None	None taken	85%	4,400,000	14,800	93%	No	None taken
14	None	None taken	90%	4,500,000	7,100	72%	No	None taken
15	None	None taken	48%	2,610,000	16,000	87%	Occ. RBC	None taken

One may also find evidence of an enlarged heart (if there has been pre-existing hypertension) [6, 13] and an increased area of supracardiac dullness,[6, 13] if the dissection involves the first portion of the aorta. If there has been bleeding into the pleural cavities, one will find the signs of a pleural effusion.[37] This is most commonly found on the left side.

A friction rub [7] is usually not found although there have been cases reported in which it was present.[17] Levine states that he often uses the absence of this finding to differentiate a dissecting aneurysm from a myocardial infarction. A friction rub was not noted in any of our cases.

Other signs and symptoms will vary, depending upon the vessels involved. Dissection of the following arteries will produce the symptoms noted:

Carotid artery: Hemiplegia; vertigo; syncope.

Renal artery [39, 40]: Pain in flank; hematuria; anuria; uremia.

Mesenteric artery [6]: Abdominal pain; diarrhea (with or without blood); signs of intestinal obstruction.

External iliac arteries [6]: Numbness, weakness, coldness and discoloration of legs.

Lumbar arteries: Bizarre neurological signs such as loss of reflexes, transient paralysis and paresthesias.[6, 42, 41] The frequent occurrence of

neurological signs results from obstruction of various lumbar and intercostal arteries with resultant ischemia of the spinal cord.

Subclavian artery: Symptoms similar to those present in the scalenous syndrome.

The laboratory findings of significance are:

Leukocytosis [17, 18, 6, 7, 16]: An increase in the leukocytes is usually present although some cases have normal counts. Thomas and Garber [18] found a leukocytosis in 45 of 48 cases and Logue [6] in eight of 10 cases. Twelve of our 15 cases had a leukocytosis of 11,000 or more. The counts varied from 11,600 to 26,000 with an average of 16,200. The percentage of polymorphonuclears varied from 72 to 93 per cent with an average of 84 per cent.

Progressive Anemia [17, 18, 7, 32]: This occurs as a result of the bleeding into the aortic wall and is not found in cases of coronary occlusion, rupture of the aortic cusps, ruptured chordae tendineae, or in rupture of the aorta into the pulmonary artery. In only one of our cases was more than one count done and this showed a 12 per cent decrease in the hemoglobin content.

Hematuria [39, 40] may occur if the renal vessels are involved.

Positive Serological Test for Syphilis: This will confuse the picture more than it aids, especially if the dissection produces aortic insufficiency. Two of our 15 cases had positive serological tests and both of these had evidence of cardiovascular syphilis at necropsy.

Roentgenological examination of the chest may or may not aid in the diagnosis of dissecting aneurysms.[17, 6, 38, 43] Wood et al.,[43] in an excellent review of the roentgenographic features of dissecting aneurysm, state that the common findings are as follows:

(1) A deformity of the supracardiac shadow. Frequently an arcuate excrescence extends outward from some point in the aortic arch. This shadow may or may not pulsate.

(2) The shadow alteration of the supracardiac shadow in successive films produced by an extension of the dissection is probably the most pathognomonic roentgenological sign.

(3) Displacement of the esophagus and trachea may occur.

(4) Often enlargement of the heart may be present.

(5) Frequently one will find evidence of fluid in the pleural cavities, especially the left.

Laminagraphic studies are of value in localizing the portion of the aorta involved,[44] but none of the roentgenological findings are pathognomonic. McGeachy and Paullin,[15] in a review of 22 roentgenograms in cases of dissecting aneurysm, found an increased aortic shadow in 16; cardiac hypertrophy in nine and pleural effusion in eight. All six of Gouley and Anderson's [38] cases had roentgenographic evidence of a dilated aortic arch. Chest roentgenograms were taken in five of our cases; an enlarged heart was noted in three cases; one had a saccular aneurysm; one had a moderate degree of

dilatation of the aorta; and one showed a widening of the mediastinal shadow on the right.

Electrocardiography will show no distinct or diagnostic pattern in dissecting aneurysm but is of great importance in excluding coronary occlusion.[17, 18, 6, 7] There have been cases reported in which the electrocardiogram showed changes similar to those found in coronary occlusion.[45, 12, 23, 12] Weiss presents a case in which the dissecting aneurysm compressed the mouth of the left coronary artery, producing a myocardial infarction of the left ventricle which was shown by the electrocardiogram. Hamburger and Ferris [23] present a case with progressive elevation of the S–T segment and inversion of the T-waves in Leads II and III with an increase in the depth of Q_3. At necropsy, ecchymosis was found about the right coronary artery, one centimeter from its origin. White et al.[46] state that they "have never encountered a case of proved severe myocardial infarction with practically normal electrocardiograms through the first week of the acute illness." If one encounters a case of severe chest pain in a patient, who may or may not have hypertension, and who, after a week of illness, fails to show any significant changes in the electrocardiogram one should think twice before labelling this patient as a victim of coronary artery disease. In cases of pericardial effusion one may find elevated S–T segments and/or inverted T-waves.

Electrocardiograms were taken in four of our cases and showed the following: one showed complete auricular-ventricular dissociation (case no. 4). At necropsy, hemorrhage was found to extend into the tissue between the pulmonary artery and aorta and into the musculature of the left atrium, extending down to the A–V line and covering the area of the S–A node and A–V bundle. In the second case the S–T segments in Leads II and III were depressed and all T-waves upright. In the third case there was slurring of the QRS in Lead III with inversion of T_3. In the fourth case there was depressed S–T segments in Leads II and III and elevation of S–T segment in Lead IV.

In a differential diagnosis one must rule out other causes of sudden severe pain such as coronary occlusion, pulmonary infarction, peripheral embolus and surgical conditions in the abdomen. Dissecting aneurysm differs from coronary occlusion [31, 12] in that the pain is usually more severe and has a wider radiation; syncope is often present; the blood pressure does not usually fall; there is no evidence of a pericardial friction rub. Sudden appearance of an aortic diastolic murmur is important; the electrocardiogram will show no diagnostic feature; and roentgenological examination may be helpful.

Summary

1. Fifteen cases of dissecting aneurysm have been reported.

2. A review of the recent literature with a discussion of the symptoms, physical signs, etiology, pathogenesis, and pathological findings is presented.

3. The diagnosis rests on clinical perspicacity and evaluation of the presenting factors.

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PSYCHOGENIC RHEUMATISM *

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A common problem in the practice of internal medicine is the patient who complains of aches and pains in the muscles and joints and chronic fatigue. Often there is slight fever but otherwise the physical examination and laboratory studies are negative. Attention is focused on this slight rise in temperature and the patient undergoes repeated and prolonged studies from the standpoint of obscure infection or endocrine dysfunction. Formerly such patients were often thought to be tuberculous; later rheumatic infection, with much attention to the heart, was suspected; nowadays chronic brucellosis is the most frequent diagnosis. In the course of the many physical and laboratory studies slight deviations from normal are detected and additional diagnoses are made which add to the patient's concern. She sees herself crippled by arthritis or heart disease and anticipates being a burden to her family. In addition to the many physical and physiotherapeutic measures that are used in treatment, rest and more rest is urged upon the patient, which perpetuates the invalidism and leads to greater restriction and a more impoverished life. This kind of a story continues, sometimes for years, often with prolonged periods of hospital observation and sanitarium stay.

These observations are based on a study of 40 patients encountered in a larger study of 200 patients with chronic fatigue, because so-called psychogenic rheumatism is only an aspect of the chronic fatigue problem. I do not care for the term psychogenic rheumatism because I am not interested in proving psychogenesis, and the term rheumatism is already surrounded with enough opprobrium without attaching to it the suspect word psychogenic. Psychosomatic does not mean to study the soma less; it only means to study the psyche more. Therefore I have been interested in studying these patients from an emotional as well as a physical standpoint to see if a relationship exists. The subject has received considerable attention in military medicine and in trying to apply the observations to civilian medicine I thought it advisable to use the term as a title although other designations, which will be mentioned, are preferable.

Of the 40 patient only five were men. All but four of the women were married. Physical findings of significance were uniformly absent. Halliday, whose observations on this subject are noteworthy, finds fibrositic nodules just as common in people who have no complaints as in those with so-called fibrositis, which is the diagnosis commonly applied to this syndrome in Great Britain. Sixteen patients had slight fever, always less than 100°,

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and in only two was there slight elevation of the sedimentation rate. Neither leukocytosis nor any other important abnormality of the blood count was found. Lowered metabolic readings were occasionally encountered and low normal fasting blood sugar levels, as well as somewhat flattened sugar tolerance curves, were rarely observed but it was always felt that these were secondary rather than causal features. The same findings were present after improvement.

Evidence for chronic brucellosis seemed positive in only one patient. Low back pain of a nagging character was a frequent association, and atypical neuralgias of the face, shoulder region, and leg, were frequently associated with the body aches and pains. "Sinus infection" was almost invariably held responsible for headache, "focal infection" for the atypical neuralgia, and slight pelvic abnormalities for pain in the back.

The referring diagnoses included arthritis, fibrositis, muscular and non-articular rheumatism; tuberculosis, rheumatic fever, and brucellosis; endocrine dysfunction, especially asthenia of thyroid and adrenal origin, adrenal cortical insufficiency being a frequent diagnosis. Hypoglycemia, low blood pressure, anemia and avitaminosis occurred again and again in almost every history. Neurocirculatory asthenia and constitutional inadequacy were frequent diagnoses. Colitis, autointoxication, and autonomic imbalance were often mentioned. If the patient was anywhere near middle-age, menopause was invariably held responsible, both in women and men, so that injections of estrogenic substance or testosterone were almost as frequent as injections of vitamin B_1.

Psychosomatic study, meaning the simultaneous application of physiological and psychological technics, proved the presence of psychopathology rather than tissue pathology. Hysteria was encountered in 16 patients, anxiety states in 11, hypochondriasis in two, and two suffered from psychotic depressions. The latter two were helped by electric shock. In nine patients I was unable to make a precise psychiatric diagnosis other than an underlying neurotic character. The one patient with rather definite evidence of chronic brucellosis, as indicated by suggestive history and high titers in the agglutination reaction, in addition to positive skin tests, had a pronounced personality disturbance which antedated the onset of the illness.

Psychological symptoms most frequently encountered were poor sleep and poor sexual adjustment, and a marital problem was the most frequent underlying problem. Significant emotional conflicts were found which were apparently responsible for the fatigue, but the special feature associated with muscular aches and pains was the presence of chronic resentment of which the patient was usually totally unaware.

Diagnosis

Psychosomatic diagnosis means more than diagnosis by exclusion. It means the utilization of physiological and psychological technics simultane-

ously in preparation for comprehensive medical care. We do not have to change our history form—we only have to change our point of view. Diagnosis by exclusion is dangerous in these cases and leads to greater invalidism. The physician becomes a pathogenic agent in perpetuating the illness by his well meaning but mistaken and never-ending efforts to find a "physical cause." The problem is not so complicated that we cannot complete our physical studies with dispatch and at the same time make psychological observations.

Therefore, one may follow the standard form of history taking but in accordance with what has already been said more attention will be paid to the behavior of the patient and to the actual words that he uses in describing his complaints as well as the asides and apparent irrelevancies that so often give important clues to the emotional factor. Other fundamental considerations are to give the patient time, allowing him to talk with as few interruptions as possible; avoiding extensive note-taking so that the patient may feel that you are more interested in him as a person than in the setting down of the history; showing interest and sympathy for what the patient sometimes regards as trivial or silly; paying more attention to the chronological development of the life history with emphasis on the various factors in the childhood period that may have influenced the development of the personality; giving special attention to puberty and adolescence with the frequent emotional problems of that period; paying attention to the epochs and crucial periods in life when psychosomatic disturbances are apt to arise; and, particularly, obtaining a more complete picture of the family background.

Just as we try to establish a kind of Koch's postulate for an allergic problem, hay-fever for example,

(1) heredity
(2) seasonal history
(3) skin tests
(4) antibodies
(5) induction of an attack with pollen
(6) hyposensitization or avoidance of offending substance in controlling attacks,

so in the psychosomatic problems we try to establish,

(1) the family history (heredity and pseudo-heredity)
(2) evidence for a childhood neurosis
(3) sensitivity to specific emotional factors (temporal relationship of present illness and emotionally disturbing event) especially at epochal or crucial life periods (puberty, marriage, childbirth, climacteric, etc.)
(4) a specific personality structure (other evidence of neurosis or character disturbance)

(5) demonstration of specific behavior on taking the history (artificial exposure to a conflict situation)
(6) hyposensitization by psychotherapy or the avoidance of the provocative situation.

We will not be able to establish all of these postulates in every case. For example, evidence for a childhood neurosis will often be lacking—neither the patient nor his family can recall disturbed behavior or bodily dysfunction. But if we adhere to these criteria we can establish the diagnosis on positive data from an emotional standpoint at the same time that we are making negative observations from a physical standpoint.

If we listen as carefully to what people say as to the sounds that their hearts make, we will often find that they express their problem in symbolic language. Thus a middle-aged, frigid woman married to a rather immature man, whom she compared to his arrogant father, asserted "when pop sticks out of him it's war with me." Another patient whose ache was in her life situation—for years she had been a martyr to a sick and demanding mother—spoke of "being one big pain from head to toe." An hysterical woman who suspected that her fading charms would no longer hold her husband's affections spoke of her "feverish love" for him. Again and again we find these patients "burned-up" with resentment and "aching" to express their unappeased hostility.

Psychopathology. Nowadays lack of energy is apt to be explained by lack of vitamins; but, while these patients are sometimes too tired to eat and may not get an adequate diet, this is certainly not their primary problem. What we must interest ourselves in is not so much a lack of vitamins but the lack of emotional satisfaction in their lives. There must be some kind of a balance to the emotional life—too much expenditure on conflict with too little satisfaction coming in and the patient is headed for emotional bankruptcy.

In the same way instead of looking for focal infection we had better look for focal conflict and often we will find it in regard to a marital or parent-child problem. Emotional conflict, which uses up energy that is then no longer available for work or social purposes, is the commonest cause of chronic fatigue. The special feature of the patients with muscular aches and pains is the presence of smoldering resentment. Usually they are not aware or are only dimly aware of it, but when it is brought to the surface and their feelings somewhat relieved improvement takes place. As Sherrington expressed it, the best way to deal with tension of emotional origin is action, the next best way is by speech and the least effective is by thought, which means that if people have tension of emotional origin and can do something about it, punching someone they dislike, for example, or telling him off, they often relieve their tension, regardless of other consequences. But the person who says, "Oh, what is the use of fighting; after all, she is my mother, sister, daughter"—that person, who does not realize the amount of

aggravation in her day-to-day existence and certainly does not know how angry it makes her or what hostile feelings she is accumulating—that kind of a person is unable to relax and her rebellion takes the form of constant muscle tension. If we stop to think for a moment it is clear why this should be so. As Ellman et al. point out, the muscles serve as a means of defense and attack in the struggle for existence and thus internal tension is most easily relieved by muscular action. When the external expression of aggression in the form of muscular action is inhibited by repressing forces, then muscular tension may result which is felt by the individual as pain and limitation of movement and is often erroneously interpreted by the examining physician as fibrositis or muscular rheumatism. In Ellman et al.'s study of 50 civilian and military cases labelled as fibrositis, 35 suffered from common psychological disorders bearing on and of probable etiological significance for their complaint. Twenty-five of the 35 were classed as hysterical conditions, seven as anxiety states, and three as depressive states. More recently Boland and Corr found psychogenic rheumatism to be the most frequent cause of disability in 450 consecutive cases diagnosed as arthritis or allied organic conditions in an army general hospital. Approximately one third of the patients in the entire series were considered incapacitated because of psychic difficulty. The sedimentation rate was normal in all cases and in one third of the cases there was a history of invalidism or semi-invalidism from rheumatism in one or more members of the immediate family.

An outstanding characteristic in their patients with psychogenic backache was persistence of disability in spite of prolonged bed rest. They emphasize this feature of the disability in dramatic fashion when they cite the patient with advanced active rheumatoid spondylitis who was found pushing another with pure psychogenic backache to the post-exchange in a wheel-chair.

Halliday has been chiefly responsible for calling our attention to this important syndrome in civil medicine. Working as medical referee with the insured population of Scotland, he surveyed a series of 145 consecutive patients labelled "rheumatism" (including fibrositis, lumbago, sciatica and neuritis), and found that 57 of them (i.e., 39 per cent) were incapacitated because of psychoneurosis. Thirty-seven per cent of an additional similar series of 62 patients examined by the same author were regarded as being disabled because of psychoneurotic disturbances. The incidence of "psychoneurotic rheumatism," he says, rises still further—to 40–60 per cent—if only those patients are considered who have been on the sick list for two months or more.

Elsewhere the significance of organ language has been pointed out.[10] When the individual is unable to express his tension by word or deed, his body sometimes takes over the function of saying things for him that he cannot say with his mouth. Thus the individual who is unable to swallow, in the absence of organic disease, sometimes cannot swallow something in his life situation and in the same way the individual with muscular aches and

pains would often like to express his aggression against someone in particular but is prevented from doing so by the affection or respect for that person that is mingled with his hostility. Hence, persuading such patients to talk about focal conflict may provide an answer to the problem.

Another very satisfactory way to get people to discuss themselves in relation to their illness is to use a case illustration. Repeatedly this is effective when other methods of trying to make people see the relation between emotions and illness fail. If one can think of an apt case illustration, the patient can readily identify himself and, even where there are marked divergences, the patient will often see a partial application which will encourage him to talk about his personal life. Sometimes he will deny the application only to go on from that point to discuss emotional factors of importance which previously he was unable to think of.

I do not know the cause of the slight fever such cases often present but I do not look upon it as significant. Reimann's study of the problem of long-continued, low-grade fever concerned 16 women. In them he found a high incidence of neurosis. He concluded that a certain proportion of normal individuals have temperatures regulated at levels slightly higher than 98.6° and that temperature of these levels is often found in neurotic persons. Certainly it is a mistake to focus the attention of the patient on this slight fever as an indication of "an obscure infection" to which we must devote our attention "until the cause is found." Nor is it necessary to call it psychogenic. In other words, in regard to this whole problem I prefer to regard the physical and psychological aspects as but different phases of the disordered constitution, perhaps parallel manifestations of the same basic fault, existing together and related to one another. In other words, psychological forces and somatic manifestations may have their roots in the same unconscious processes which discharge partly on the level of psychic representation through thoughts and feelings and partly on the physiological level through the autonomic nervous system. We know, for example, that slight disturbances in temperature regulation occur throughout the menstrual cycle, especially in some women, and these patients seem to be especially sensitive in this regard. Moreover, as Flind and Barber point out in a study of this disorder among Royal Air Force Personnel, there seems to be a lowering of the threshold for the appreciation of bodily sensation in some cases of neurosis. This leads me to say a few words regarding "constitutional inadequacy" which I look upon as a very unfortunate term. Most of these patients are not constitutionally inadequate even though, as one stated, she was always "a tired and achy" person. As Dunbar has pointed out, we must distinguish between pseudo-heredity and pure heredity. The child who grows up with a chronically sick and tired mother is apt to identify herself unconsciously with her mother and, despite contrary conscious efforts, will often repeat the pattern of the mother's life. In other words, if we look to the environment, to the family group especially, for the origin of these psychosomatic disturbances, we will often find emotional con-

flicts, and by bringing the material to the surface, and dealing with it in a more realistic way we can sometimes help them to become useful citizens again, instead of labelling them constitutionally inadequate or burdening them with that other equally unsatisfactory term, neurocirculatory asthenia, which is usually just a name to cloak our ignorance of the life situation of the individual.

The same strictures apply to the various symptom diagnoses that are often made in the study of these patients and to which too much attention is paid, increasing the anxiety of the patient. Slight anemia, somewhat lowered blood pressure or basal metabolism, somewhat depressed fasting blood sugars or even flattened blood sugar curves, intimations of endocrine dysfunction as a result of more elaborate hormonal assays, only perpetuate the invalidism. In other words, the physician often becomes a pathogenic agent when he approaches these patients purely from an organic standpoint and stresses insignificant physical or physiological deviations.

Probably the most difficult problem at the present moment is the question of chronic brucellosis. We are warned again and again that we must not make a diagnosis of neurasthenia, which under such circumstances is a psychological term without psychic meaning, until we have ruled out the possibility of chronic brucellosis. It is unquestionably true that chronic brucellosis occurs and produces a clinical picture not unlike the one we are describing but in the first place we ought to be able to establish that diagnosis with some certainty and without too much delay and secondly we must not forget, as Harris points out, that the two disorders—brucellosis and specific forms of psychoneurosis—may coexist. In this connection I would like to say that the emotions often exploit an organic illness and thus it is that frequently in connection with an infectious disease or after operation, convalescence lingers and invalidism sets in. Repeatedly our patients tell us that "they haven't been the same since their child was born—they gave all their strength to the baby," or "they haven't been right since an operation," especially a pelvic operation. Or the illness began following a slight respiratory infection. The belief is widespread that the organic disease produced the neurosis, whereas the actual mechanism is that the organic process has broken down the individual's psychological defenses, regression occurs, and the individual's predisposition, determined by his personality structure, permits the neurosis to emerge.

A contrary aspect of the relation of organic disease to neurosis is the severe neurotic disorder, hypochondriasis, for example, in which the patient is obsessed with his neurotic symptoms and inattentive to some serious disorder. I have frequently observed that the patient who insists "that his illness is physical" is apt to be suffering from a disorder of emotional origin while the patient who is eager to blame it on the psyche often has an organic disease.

Treatment

In approaching the patient from the standpoint of psychosomatic diagnosis one must realize that in dealing with the emotions one cannot separate treatment from diagnosis and that really as soon as one has made an initial contact with the patient the groundwork is being prepared for treatment. There can be no sharp division between the period of diagnosis and the period of beginning treatment.

I would urge that the physical aspects of the study be completed as quickly as possible. One of the great difficulties about the organic approach in medicine is that we can always think of another process—obscure infection, hormonal disturbance, metabolic or allergic disorder—that we must continue to investigate and hence it is that these patients go through repeated and prolonged periods of observation, each one adding to the difficulty by focusing attention on a part rather than on the whole. This applies especially to brucellosis which is a particularly vexatious problem at the moment because so many patients get skin tested that the tests themselves induce immune reactions resulting in low titre agglutination responses.

I would also urge, once we have satisfied ourselves that the slight temperature elevation is only an insignificant phase of the disorder, that instead of suggesting to these patients that they keep a record of their temperature we tell them to stop taking it. Sometimes the desire is so pronounced that they have to be told to throw their thermometer away.

Once we have excluded physical disease and done it expeditiously we can say to these patients that they have no evidence of organic disease, and often it is wise to add at this point, or a little later, that neither do they have evidence of mental disease because so often with lay misconceptions regarding emotional problems, to suggest that the disorder is emotional means to the patient that it is mental and that he may be in danger "of losing his mind."

I always ask the patient toward the end of the study, "what have you thought about the cause of your illness?" We will often be amazed at the extraordinary ideas that these patients have had, some of which they have themselves contributed from their reading or fantasies and some of which have been supplied by the many medical examinations and investigations that have been done. The first rationalizations of anxiety have to do with "chronic and crippling arthritis which is going to make a life-long invalid of me, and thus I will become a burden to my family." Often they are thinking about heart disease because of the suggestion of rheumatic infection and the attention that the physician pays to the heart; of an obscure infection; of "autointoxication" or "blood poisoning," or of syphilis or even of cancer. Because of their inability to concentrate or because their memory plays them tricks they have the fear of losing their mind and often associated with it suicidal thoughts which are very distressing. We can make no headway with these patients from a treatment standpoint until we have these first

layers of anxiety out on the surface. It is like the layers of an onion; as they are peeled off, new problems present themselves and these new problems will invariably be found within the family group. Marital incompatibility and sexual difficulties are almost always present but the patients often hesitate to discuss them because they regard them as personal problems unrelated to their illness.

When we say to these people that their aches and pains and fatigue are due to the fact that they are always in a state of tension, that they do not know how to relax, even at night, and that because their muscles are taut they are crying out in protest with aches and pains, it makes sense to them and provides a stepping stone for them to begin to talk about their emotional problems. To some people I may make the additional suggestion that, after all, emotional immaturity is the background of a psychosomatic disorder and that "growing pains" that occur later in life are apt to be more painful than when they occur early in life.

Chronic resentment—smoldering discontent—is the special emotional problem in these patients but it had better be approached indirectly. One must avoid the crude suggestion that they are angry at someone who is supposed to be near and dear to them or for whom they are supposed to have filial respect. That problem can be approached by gradually making the patient aware of the discontent and chronic aggravation in his life as we study his day-to-day existence and note how his tension increases finally to the point where symptoms appear.

In other words, we must let them see that they are suffering not from disease of body or mind but rather from a disorder of their feelings. Then they will often tell you how "burned up" they have been and of the really great amount of hostility that has been dammed up behind a surface complacency.

Instead of cautioning rest and more rest, which only permits these people to "stew in their own juices," I recommend "that they carry on in spite of symptoms" and this they will often be able to do once they have divorced their pain from the fear of arthritis, heart disease, cancer or what not. Once neurotic pain is divorced from a fear of organic disease, it is remarkable how rapidly it will disappear or diminish. At the same time I recommend that they do not talk about their illness to their friends but try to cultivate the atmosphere of health by telling people that they are well no matter how badly they feel. As soon as possible I try to get them away from injections of vitamins and hormones, from sedatives and even physiotherapy, or if some of these measures are continued I make it clear to them that they are being used in a supplementary capacity and that the cure lies in emotional re-education. Halliday has called attention to physiotherapy and fixation of symptoms in his insured patients and we see the same thing in private and hospital practice. It is of course sometimes necessary to make certain concessions to the previous organic miseducation that the patient has had. We cannot go too quickly in changing our approach from disease to disorder,

from the idea of doing something for the patient to having him do something for himself, from education along physical lines to the necessity for emotional growth. The essence of the psychotherapy, which should be a part of the equipment of every physician, is not to go faster than the patient is prepared to go, because as Lindemann has said, clumsy psychotherapy can be as dangerous to the social life as poor surgery is to the physical life.

In connection with physical medicine I think one more word ought to be said and that is the problem of belts, braces and supports. So often we find these patients wearing sacroiliac or abdominal supports when what they need is inner support. Instead of trying to bolster them up with a crutch what we ought to do is try to develop their inner, emotional security so that they won't have to lean on supports, or braces, or for that matter on their physician.

Just as in a consideration of somatic disease it is necessary to make a complete diagnosis before we can hope to apply scientific treatment, so in psychosomatic medicine it is equally necessary. Hence, just as in general medical teaching we have always emphasized etiologic, anatomic, and functional diagnosis, so in psychological medicine, as pointed out by Levine, it is necessary to make a clinical, dynamic, and genetic diagnosis before one can stand on safe ground in regard to psychotherapy.

The clinical diagnosis in psychosomatic medicine refers to the structural and physiological deviations as well as to the underlying or associated psychological disturbance. For example, in this syndrome we would like to know whether we are dealing with a mild personality disorder such as hysteria or a severe personality disorder such as hypochondriasis. From the standpoint of the physician-patient relationship it is important to know whether the symptoms are on the basis of conversion hysteria or a part of the clinical picture of depression in which the mood disturbance is overshadowed by the somatic complaints. When one deals with depression there is often the threat of suicide.

Dynamic diagnosis refers to the meaning and purpose of the symptoms in terms of behavior. Coupled with the genetic diagnosis, which is derived from the longitudinal survey of the individual life history, we are then in a position for comprehensive medical care.

Instead of calling this psychogenic rheumatism, fibrositis, or even muscular rheumatism, the most suitable diagnostic term, as Flind and Barber point out, is the psychiatric diagnosis applicable to each case because it is the psychopathology that is chiefly responsible for the syndrome and it is by means of psychotherapy that we can deal with these patients most effectively.

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A STUDY OF MITRAL STENOSIS IN PATIENTS WHO SURVIVED THE AGE OF FIFTY*

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Few studies have been made of mitral stenosis in persons who have passed middle life, although many excellent papers have been published on the natural history and course of rheumatic heart disease in over-all age groups and in young people. In only a few of these writings has the material been so arranged that information pertaining to older patients is available. We have found no paper which confines itself to mitral stenosis as the only existing valvular lesion in patients of advanced age. Boas and Perla [1] discussed mitral stenosis after 50 but included combined valvular lesions. For a number of years, one of the authors (L. A. B.) has been interested in the characteristics of rheumatic valvular disease in the older patients. As a result, this study of isolated mitral stenosis in patients who survived the age of 50 has been made. Particular attention was paid to the history of rheumatic fever, age of occurrence, time intervals relative to the onset of symptoms, congestive failure, and death. The diagnostic findings, complications, and mode of death are other points which have been of interest.

Material

The material used has been collected from patients whom we have studied during the past four years at this Hospital, plus patients seen in private practice. The vast majority of the patients seen by the Cardiac Service of this Hospital during these years were veterans of World War I, whose average age approached 50. The large amount of cardiac material seen in this relatively limited age group permitted us to assemble this series of cases. No patient was included who was not known to have survived the age of 50.

The clinical diagnosis was based on the typical diastolic murmur at the apex. No living case was included in which the character of the murmur was questionable. Two cases are included in which no such murmur was heard during life, but isolated mitral stenosis was demonstrated at autopsy. All but one of these patients were examined by one or more members of the Cardiac Section, and in this instance, the diagnosis was verified at post mortem. Since mitral stenosis in these older patients is frequently associated with disease of other valves, careful attention was always given to this

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point. All cases were eliminated in which there existed any such suggestion. On the basis of these criteria, we were able to select 106 cases from our files. All but two of these patients were males.

The frequency of mitral stenosis in patients beyond the age of 50 is not easily determined from the literature. Cohn and Lingg [2] found that only 16 per cent of the patients with rheumatic heart disease included in their series lived beyond the age of 45. Willius [3] indicates that only one of 124 patients with mitral disease lived past the age of 50. These data would indicate a lower incidence than the reports of other authors. Samways [4] found the average age at death in 196 patients to be 38, but 10 per cent lived beyond 60. Cabot [5] indicates that 30 per cent of his cases of mitral stenosis passed 50 years of age. Boas and Fineberg [6] studied the correlation of hypertension with mitral stenosis in 135 patients, 46 of whom were over 50. Levine and Fulton,[7] in a similar study of 762 patients, show 54 of the series to be over 50 years of age. In the series studied by Horns,[8] 91 of 144 cases were 45 or past. Stone and Feil [9] discuss 100 autopsied cases of mitral stenosis (46 per cent combined lesions), of whom 28 were past 50 years of age. Clawson [10] indicates indirectly in his statistical study of autopsy material that approximately one-third of those with mitral disease alone lived beyond 50. White and Bland [11] have drawn attention to the fact that mitral stenosis may occasionally exist in the very aged. The conclusion of Levine and Fulton [7] that approximately 20 per cent of those with mitral stenosis live beyond 50 seems justified. No conclusion can be gained from our material since it is made up of a relatively fixed age group.

History of Rheumatic Fever

A definite history of rheumatic fever was elicited in 31 cases; a history of chorea was noted in one patient. Only definite, acute, multiple joint involvement and chorea were considered as manifestations of rheumatic fever. The less typical manifestations were so difficult to evaluate in these older patients that they were not included. In nine cases, the records contained no information relative to this point, therefore, a definite history of past rheumatic infection was established in 32 of those patients upon whom information was available. This is a considerably lower incidence than that usually reported: DeGraff and Lingg [12] obtained a history of rheumatic fever in 70 per cent of their cases, while Hedley [13] reported a positive rheumatic history in 66.2 per cent of 916 fatal cases of rheumatic heart disease. White [14] found that about 75 per cent of such patients have a positive rheumatic history. Levine [15] gives a somewhat lower figure of approximately 50 per cent. A history of rheumatic fever was present in 56.6 per cent of 100 autopsied cases of mitral stenosis studied by Stone and Feil.[9] The above statements were based on studies of clinical material, in which the average patient was much younger than those included in this study. Boas and Perla [1] found the incidence of positive rheumatic history to be nearly identi-

cal with our findings in a series of cases of similar age. It may also be pointed out that studies of aortic stenosis, which involves similar age groups, discloses a positive history of rheumatic fever in 30 to 50 per cent of the cases.[16, 17, 18]

It seems that the history of previous rheumatic fever can be established much less frequently among the older patients. In part, this may be due to faulty memory; however, it is our impression that a well-defined attack of rheumatic fever causes sufficient distress and prolonged morbidity so that it is rarely forgotten.

The initial rheumatic attack occurred before the age of 20 in 18 of the 31 patients; it occurred before the age of 10 in 7 and after 30 in 2, the oldest being 40 years. The average age at the initial attack was 18 years. Two acute episodes had occurred in seven patients. The average age at the time of the initial attack in these 32 patients was approximately 10 years greater than that reported for over-all age groups. Bland and Jones[19] found this average age to be eight years. Stroud et al.[20] were in essential agreement while Cohn and Lingg[2] state that the onset of the disease occurred before the age of 15 in 70 per cent of their series.

There is some difference of opinion expressed in the literature regarding the relationship of the later onset of the disease to the ultimate course. The papers of DeGraff and Lingg[12] and Davis and Weiss[21] are quite definite in the implication that the later the initial infection, the shorter the course of the subsequent heart disease. Cohn and Lingg[2] concluded that the later onset was favorable to a somewhat longer course. The data included in the discussion of auricular fibrillation by Stroud et al.[22] would indicate that on the average the duration of the disease was longer in persons in whom the initial infection occurred after the age of 20. DeGraff and Lingg[12] found the mean duration of the disease to be 15 years with 75 per cent under 23 years. Davis and Weiss[21] indicate that only one-fourth of the cases studied by them lived over 25 years and state that the duration was 30 per cent longer if the initial infection occurred before the age of 10 years. Cohn and Lingg[2] found the average duration to be slightly under 13 years.

The duration of the disease in this group of patients was unusually long. For those patients who are dead, the average duration was 37.5 years, while the disease had existed in those still living an average of 32.9 years. It is apparent that the later age of initial infection (18 years) did not prevent the disease running a long course. The advanced age of these patients is accounted for the most part by a long course of the disease rather than by a late onset.

Pathological studies indicate that most persons who live past middle age with rheumatic heart disease have had the affliction for a long time, since evidence of rheumatic activity is rarely found at autopsy. Console[23] in his very excellent study on this point noted evidence of activity was rare in patients dying after 40 and only three of 24 patients dying after 50 had such evidence. de la Chapelle et al.[24] also indicate that evidence of rheumatic

activity is comparatively infrequent after the age of 40. Davis and Weiss [21] point out that the longer the duration of the disease, the less frequently is evidence of rheumatic activity found. It seems reasonable to conclude that most of those patients who reach advanced age with mitral stenosis have lived with the condition for many years and that the rheumatic process has become inactive. The uniform results of pathological studies sustain this view. If a late onset of rheumatic infection were responsible for the advanced age, then it would be expected that evidence of activity would be found much more frequently in autopsy material.

It is also of interest to speculate as to the significance of the frequent absence of a history of rheumatic fever among these patients. While faulty memory may be a factor, it does not seem that it can be held responsible for more than a small fraction of the discrepancy. It has been our impression that the majority of these persons never did have typical rheumatic fever, but that they did have atypical infection. This did not result in definite joint involvement or chorea, but during the course of the infection, the heart was involved. Though such a situation has for a long time been considered probable, the recent work of Rantz et al.[25] furnished objective support to this conception. They have noted conclusive electrocardiographic signs typical of rheumatic fever in patients following streptococcal infections without any evidence of joint involvement. They also noted similar changes preceding the onset of joint symptoms. If it is assumed that such a large proportion of the mitral stenosis cases in this age group have sustained their cardiac damage through this atypical type of infection, it is also possible that the advanced age to which they live is dependent, in some manner, on the characteristics of the initial infection. This might be explained on the basis that the cardiac involvement under such circumstances is comparatively mild, and for the most part, is confined to the endocardium insofar as permanent irreversible changes are concerned. Under such circumstances, valvular deformity could develop over a period of time without there having occurred any significant myocardial damage. The development of definite stenosis as a result of slow fibrosis might take a period of several years. Heart failure would not be expected to occur in early life under these circumstances. It has been established that the deaths from rheumatic heart disease follow a bimodal curve, those occurring before 40 being, for the most part, associated with active myocarditis, while the later deaths are due to the dynamic effects of the valvular lesions.[23, 26] The group under discussion would then represent those patients who escape significant myocardial injury but develop, after considerable time, definite evidence of valvular disease and may after years go into heart failure as the result of the hydro-dynamic effects of the valvular lesions.

This same reasoning can also account for the long duration among those patients who gave a previous history of definite rheumatic infection. Bland and Jones,[27] in considering the delayed appearance of heart disease among young people following acute rheumatic fever, have expressed the opinion

that continued rheumatic activity is necessary. It does not seem to us that such is essential since, as previously stated, valvular deformity might develop as the result of gradual fibrosis over a period of time in the absence of any recurrence of activity.

It has been our impression that from the viewpoint of cardiac disease, the line dividing rheumatic from non-rheumatic-type infections cannot be definitely drawn. The findings of Rantz et al.[25] have already been cited. There have been many papers published which refer to the abnormal electrocardiograms occurring in patients suffering from streptococcal and other types of infection.[28, 29, 30] The question as to how often such findings are due to a process identical with rheumatic heart disease cannot be answered. We are inclined to agree with Rantz et al. in the view that following streptococcal infections the process may be identical with that following typical rheumatic fever. A long term follow-up of such cases will be necessary to determine how often chronic valvular lesions develop.

Clinical Course

In studying the clinical course of these patients, it was thought that the age at which the patient was first informed of the presence of heart disease might be of interest. Only nine patients had such knowledge before the age of 30 and only one of these before 20. In 84 cases, this knowledge was acquired after the age of 40 and 45 of these were 50 years of age or over, at the time. In the great majority, the diagnosis was first made at the time a physician was consulted because of cardiac symptoms. However, in 34 patients the diagnosis was incidental to physical examination for some other reason. In two cases, the diagnosis was first made at autopsy.

The age at which clinical symptoms became manifest was also late. There were a number of patients who had complained of various subjective symptoms over a period of many years. It is difficult to decide whether these complaints were of functional or organic origin. In only four persons did the symptoms begin before 30. In 10, the onset was in the fourth decade, in 41 in the fifth, while in 31, symptoms first appeared in the sixth decade. Two patients first became symptomatic after reaching 60, while 18 never admitted any cardiac symptoms. Therefore, a total of 50 patients reached the age of 50 years without subjective manifestations of heart disease. The average age at the time symptoms appeared in the 88 patients was 46.2 years. Occasionally many years elapsed between the diagnosis of valvular disease and the onset of symptoms. In four of these patients, this period ranged from 18 to 25 years. These facts emphasize the comparatively benign character of the valvular disease in these patients.

The nature of the symptomatology did not differ from that noted in mitral stenosis in general. Shortness of breath, palpitation, and fatigue were usually the first symptoms noted. Exceptions occurred in four instances where hemiplegia, vertigo, hemoptysis, and acute coronary throm-

bosis were the first manifestations. Congestive heart failure had occurred in exactly one-half [53] of these patients up to the date of our last information.

Hemiplegia was common, having occurred in 13 patients. This was probably an embolic manifestation in most instances and related to the high incidence of auricular fibrillation. However, five of these patients were never known to have had auricular fibrillation. Neither did they have hypertension.

Both subacute bacterial endocarditis and clinical evidence of coronary disease were rare. Each condition was noted only once among the 106 cases. Levine [31] has stressed the fact that subacute bacterial endocarditis is rare in the presence of advanced mitral stenosis and auricular fibrillation. The same author [32] emphasized the infrequent association of coronary disease with mitral stenosis.

Of particular interest has been the frequent association of chronic nontubercular pulmonary disease with mitral stenosis in these older patients. Not infrequently such patients may present themselves with symptoms and clinical findings typical of chronic asthmatic bronchitis. In 29 patients of the present series, the pulmonary findings were sufficiently impressive to be included in the final diagnosis. The diagnosis was emphysema in 22, pulmonary fibrosis in five cases, while the diagnosis of chronic bronchitis was made twice. The chest roentgen-ray plates were available in 81 cases. A review of these disclosed evidence of emphysema or abnormal bilateral fibrosis in 66 instances.

Parker and Weiss [33] have given an excellent description of the structural changes brought about in the lungs as a result of the chronic pulmonary hypertension and congestion resulting from mitral stenosis. They demonstrated subintimal thickening with fibroblastic proliferation, as well as both intimal and medial thickening of the small vessels. Marked changes in the alveolar walls interfere with gaseous exchange and cause stiffening of the lungs. Gouley [34] has stressed the rôle of repeated episodes of pneumonitis and infarction in bringing about chronic pulmonary interstitial changes which interfere with normal respiratory efficiency. Ferguson et al.[35] have discussed the vascular changes which are responsible for hemoptysis. It is obvious that the pulmonary pathologic changes incident to long standing mitral stenosis can be responsible for a severe degree of dyspnea, cough, wheezing, and hemoptysis. It has been our impression that these manifestations are more frequently noted among these older patients.

The associated pulmonary changes also add to the difficulty of diagnosis. The presence of emphysema tends to suppress the intensity of the murmur of mitral stenosis, while the noisy wheezing breath sounds further handicap auscultation. Under such circumstances, very careful examination may be necessary to detect the diastolic murmur, and it may be impossible. Another source of error is the evidence of right heart failure in the presence of marked pulmonary disease which may be interpreted as being due to chronic cor pulmonale. This is particularly true in patients beyond the age of 50.

Such a mistake was made in two of the cases in this series, the correction being made later. It is apparent that the pulmonary disease may contribute to an increase in pulmonary hypertension so that the cardiac failure may actually have a dual etiology.

The incidence of malignancy as an associated disease was quite high. Nine cases were so affected. The relatively large Tumor Service in this Hospital is undoubtedly responsible.

Forty-four of the 106 patients were known to be dead at the time these data were assembled; 47 were known to be living. Contact had been lost with 15 of the patients.

The average age at death was 52.8 years, the oldest patient being 64 years of age. In 14 cases we cannot be certain regarding cause of death since death occurred away from the Hospital. In 19 of the remaining 30 cases, death was due to congestive failure. Embolic episodes accounted for six deaths, five were cerebral, and one was renal in location. Each of the following accounted for one death: subacute bacterial endocarditis, pneumonia, carcinoma of the stomach, carcinoma of the bronchus, and carcinoma of the cecum. Therefore, in 26 of the 30 cases, death was directly related to the heart disease. The duration of congestive failure was known in 18 of the 19 cases and varied from six months to 10 years (average: three years). This corresponds to statistics recorded by other observers based on studies conducted on cases in younger age groups.

It was also impressive to note that many of these patients had engaged in arduous occupations over a period of many years. As previously stated, the onset of symptoms occurred relatively late; and this was in spite of the fact that they had been subjected to considerable physical strain. Some of those who had not developed cardiac symptoms were still very active. This emphasizes that the myocardium was capable of maintaining an excellent reserve over a long period and indicates that there exists a distinct difference in this respect in the disease as seen in these older patients and that which is prevalent in younger persons.

Physical Findings

The characteristic mid-diastolic murmur of mitral stenosis was made a requirement for the inclusion of a living patient in this series. We have included two cases in which the diagnosis was made at autopsy in which no diastolic murmur was described during life. In one of these cases, repeated auscultation had been carried out by several members of the Cardiac Section because it was suspected that such a lesion might be present. In one case, death was due to carcinoma of the cecum and mitral stenosis was an incidental postmortem finding. No special attention had been directed to the heart; and in the admission examination, no abnormal cardiac findings were recorded. Due to the basis upon which these patients were chosen, no information relative to the frequency with which "silent" mitral stenosis is encountered in patients of this age is available. It was found by Flaxman [36]

that no murmur was present in 3.37 per cent and only a systolic murmur was noted in 15.2 per cent of the series of mitral stenosis cases which he reviewed. Such statistics will vary in accordance with the frequency of the examinations and skill of the examiners.

There are several factors which are commonly present in these older people which make the detection by auscultation of the murmur of mitral stenosis more difficult. Obesity is frequently encountered and the layer of fat tends to absorb the low-pitched vibrations of mitral stenosis. Loud, harsh, systolic-apical murmurs are frequent and make the detection of the low-pitched, distant, diastolic murmur, which follows it, difficult. Such harsh systolic murmurs also tend to obliterate the "snapping" quality of the first sound at the apex. Chronic asthmatic bronchitis, emphysema, and fibrosis, also impair the efficiency of auscultation. A very important factor is the failure to consider the possibility of mitral stenosis in the older patients which results in inadequate auscultation.

Cardiac enlargement was definite in the majority of the cases. A review of the roentgen-ray findings disclosed 68.4 per cent of the cases showing definite cardiac enlargement. Borderline hearts were placed in the normal group. The degree of cardiac enlargement was frequently quite marked when compared to that usually seen in young persons with stenosis of the mitral valve alone. This was usually due to the prominent left ventricular enlargement. It is believed that the tendency toward left ventricular enlargement and the frequency of loud, harsh, apical-systolic murmurs are related. In turn, both of these may be related to the characteristics of the evolution of valvular lesions in these older patients. The relatively low grade rheumatic infection may cause a slow progressive deformity in which adherence of the cusp margins is less marked. As a result, mitral insufficiency becomes a prominent physiological component. This situation existing over a period of years may well account for the fact that the left ventricular enlargement is greater than that usually seen in the more rapidly developing, tight, mitral stenosis common to younger people.

Hypertension also plays a part in the left ventricular enlargement, though it was not present as frequently in our series as in that reported by Levine and Fulton.[7] Levine has repeatedly emphasized the frequency of hypertension in these older patients with mitral stenosis. In this series, the blood pressure of only 32 patients was found to exceed 150 systolic or 90 diastolic. In only 18 did the diastolic pressure exceed 100. Levine and Fulton [7] noted that the blood pressure exceeds 150 mm. of mercury systolic and 100 diastolic in 58 per cent of cases of mitral stenosis over 45 years of age. Boas and Fineberg [6] indicate that hypertension was present in 24 of 46 patients who had passed 50 years of age. However, Horns [8] noted hypertension in only 30 per cent of the patients 45 years of age or over, which is comparable to this group. Among the 32 patients with hypertension, marked cardiac enlargement was present in 20. A similar degree of enlargement was noted in only 21 of the 75 patients with normal blood pressure.

The rhythm was a regular sinus mechanism in 45, while chronic auricular fibrillation existed in 60 patients. Persistent auricular flutter was present in one case. Lewis [37] stresses the fact that the frequency of auricular fibrillation increases with age among patients with mitral stenosis. White [14] states that over 50 per cent of adult cases of mitral stenosis have auricular fibrillation. Boas and Perla [1] noted this arrhythmia in 56.5 per cent of 47 patients with mitral stenosis who were past 50. Garvin [38] found auricular fibrillation to be more frequent among older patients with rheumatic heart disease; however, his statistics reveal an incidence of 44 per cent among patients over 50 as compared to 51.2 per cent for the entire series. de la Chapelle et al.[24] also found the incidence increased among the older patients.

It is our impression that the auricular fibrillation of mitral stenosis is more closely correlated with auricular distention than with any other factor and that its incidence increases steadily with the period of time over which auricular strain has been present. There was a definite history of rheumatic fever in 14 of the patients who had auricular fibrillation. The elapsed period from this date to death or last examination was 32.2 years. Brill [39] has expressed a similar opinion relative to the etiology of this arrhythmia in association with coronary disease.

The relation of auricular fibrillation to embolic manifestations in patients with rheumatic heart disease has been stressed by Weiss and Davis [40] and by Harris and Levine.[41] Such a relationship was not striking in this small series. Only 10 of the 18 patients who suffered from definite embolic episodes had auricular fibrillation.

The character of the heart sounds was not significantly different from that usually noted with mitral stenosis. The first sound at the apex was accentuated in 72 of the 99 patients in whom the description of sounds was recorded. The pulmonary second sound was considered to be accentuated in 33 instances, while the aortic second sound was described as accentuated in five patients. The quality of the first apical sound was of diagnostic value in these older patients. The "opening snap" of the mitral valve should be mentioned. Margolis and Wolferth [42] have pointed out its value in diagnosis. It was occasionally of value in this series of cases particularly when the patient was first seen in the presence of rapid auricular fibrillation.

Diagnosis

It is generally agreed that diagnosis of mitral stenosis is fundamentally dependent upon hearing the characteristic murmur. The variations in the murmur have been described by Lewis,[37] White,[14] and Fishberg.[43] There is nothing to add but we wish to emphasize that the murmur may be audible only in a localized area and also that auscultation must be carried out with mitral stenosis in mind. We have already discussed factors commonly present in the older patients which add to the difficulties of auscultation.

There is one other point which bears some comment. Fisher [44] and

Wood and White [45] years ago discussed the mid-diastolic rumble heard in older patients with enlarged hearts while in failure. More recently others have made similar observations.[46, 47] In our experience such murmurs are not uncommon when auscultation is done carefully with the patient reclining on his left side. These murmurs, while definite, do not usually have the typical characteristics of mitral stenosis. They are usually somewhat higher in pitch, softer and less rumbling in quality. Likewise, the sharp presystolic crescendo quality is lacking in the presence of sinus rhythm. However, these points are of little practical value since in mitral stenosis the murmur may lose its characteristic attributes or become inaudible during congestive failure. It is our impression that this occurs more commonly among the older patients. When a patient is first encountered in congestive failure and such a diastolic apical murmur is present, it is impossible to be certain as to the existence of mitral stenosis. However, as compensation is restored, the murmur increases in intensity and becomes more characteristic in the presence of organic mitral stenosis, otherwise it fades away with restoration of compensation.

A sharply accentuated first apical sound in the presence of congestive failure favors mitral stenosis since in the degenerative types of heart disease this sound is commonly of poor quality and of less intensity than the second heart sound. This principle may be altered in mitral stenosis, however, if there is present a loud harsh systolic murmur which tends to obscure the first sound. Accentuation of the pulmonary second sound is of no value in the presence of congestive failure unless it is marked. The "opening snap" of the mitral valve, if present, is of value under these circumstances.

The roentgen-ray films of the chest were reviewed as to their value in the diagnosis of mitral stenosis. In 36 of the films, the cardiac configuration was found to be quite typical of mitral stenosis. In eight instances there was some prominence of the pulmonary conus which was suggestive of this diagnosis. The remainder were of no diagnostic assistance. We do not have adequate data on the fluoroscopic findings to be worthy of comment.

Electrocardiograms had been made on 104 of the 106 patients. A review of the findings revealed that there was a definite tendency toward right axis deviation in 35 instances. This deviation was marked in only 10 of the total. Left axis deviation was less common; however, quite marked deviation to the left was present in 12 persons. Hypertension was associated with left axis deviation in the great majority. In approximately one-half the cases there was no significant deviation of the electrical axis. Bundle branch block was noted in five cases, left in three, and in two, it was right. T-wave and S–T segment changes were common, most of this being due to digitalis. In two patients, the P–R interval was prolonged and in one case complete heart block existed with auricular fibrillation. The electrocardiograms did not prove to be of any great value in diagnosis. The presence of right axis deviation in patients of this age should suggest the possibility of mitral stenosis but no further help can be expected.

The most important single factor in diagnosis is the matter of bearing in mind the possibility of mitral stenosis in the older patient. There are several clinical observations which we have found helpful in suggesting this diagnosis.

1. The presence of auricular fibrillation.
2. An accentuated sharp first sound at the apex, particularly in the presence of heart failure.
3. Unusual accentuation of the pulmonary second sound.
4. A long history of chronic pulmonary symptoms; mitral stenosis should be excluded before a diagnosis of chronic cor pulmonale is made, particularly if auricular fibrillation is present.
5. Right axis deviation in the electrocardiogram even though it is slight.
6. Repeated episodes of congestive failure over a long period of time. Complaints referable to liver distention are prominent in the presence of mitral stenosis.
7. Atypical apical diastolic murmurs heard during congestive failure. These should be carefully followed.

The presence of any of the above observations should stimulate careful examination and study which may reveal mitral stenosis which might be otherwise overlooked in a patient of advanced years.

Summary

A study of the clinical course and findings in 105 patients with isolated mitral stenosis who survived the age of 50 has been made.

The high incidence of a negative history of rheumatic fever is thought to be due to these patients having suffered from atypical "rheumatic type" infections during which cardiac damage was done.

Our information indicates that the advanced age of these patients is associated with an unusually long course of rheumatic heart disease. This long course can be explained by a fundamental difference in the pathogenesis of the rheumatic process within the heart in contrast to that occurring in younger persons with a shorter duration. A relatively slight involvement of the heart limited for the most part to the endocardium and mitral valve would allow the development of mitral stenosis with the myocardium being spared. Under these circumstances, the heart is able to maintain compensation over a period of many years, and in many instances to tolerate active physical exertion.

The great frequency of symptoms and physical findings of non-tuberculous pulmonary disease was striking in these patients. It is our opinion that the longer the patients with mitral stenosis live the greater will be the incidence of chronic pulmonary disease.

The incidence of auricular fibrillation was high and is believed to be related to the duration of auricular strain. Embolic manifestations were frequent, occurring in the absence of, as well as with auricular fibrillation.

Hypertension was not as common in this group of patients as has been reported by other writers. It apparently was a factor in causing a marked degree of cardiac enlargement in many instances. It is not believed that the longevity of these patients is dependent upon the presence of hypertension as has been suggested.

Factors which are commonly present in these older patients and add to the difficulty in diagnosis are discussed. Failure to consider the possibility of mitral stenosis is thought to be the most common cause for error in diagnosis among older patients. Certain clinical observations which should suggest this possibility are outlined.

The majority of deaths in this series were due to the cardiovascular disease present. In approximately two-thirds of the fatal cases death was from congestive failure. Once congestive failure occurred, the course was essentially the same as that seen in younger patients.

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CASE REPORTS

THE CARDIOVASCULAR MANIFESTATIONS OF INDUCED THYROTOXICOSIS; REPORT OF TWO CASES *

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The occurrence of cardiovascular manifestations as results of induced thyrotoxicosis has not been commonly recorded. It is the purpose of this paper to report two cases in which the ingestion of excessively large doses of desiccated thyroid substance was associated with cardiovascular manifestations. The evidence to be presented leaves no reasonable doubt that these changes were the results of induced thyrotoxicosis.

Case Reports

Case 1. The patient was a white female 63 years old, first examined on November 26, 1940. For two months previously dyspnea, which had increased in severity, had been observed. Palpitation, nervousness and tremor had been noted for the same period. Frequency of urination was present. The medical history was irrelevant. Further questioning revealed that for two years previously 2 grains (0.13 gm.) of desiccated thyroid substance had been administered daily to the patient. The dosage, however, had been increased by the patient without consulting a physician, so that during the previous year she had been taking 8 grains (0.52 gm.) of desiccated thyroid substance daily.

The physical examination revealed an acutely ill, markedly dyspneic white female. The temperature was 98° F. (36.6° C.), and the pulse rate, which was grossly irregular, was 180 beats per minute. The blood pressure was recorded as 160 mm. of mercury systolic and 70 mm. diastolic. No palpable enlargement of the thyroid gland could be demonstrated. Moist râles were heard over the base of the right lung. No cardiac murmurs were heard. The abdomen was normal. A fine tremor of the fingers was present. Auricular fibrillation was confirmed by the electrocardiogram (figure 1*a*). Roentgenographic examination of the thorax revealed no evidence of a substernal thyroid gland. The heart was slightly enlarged; its greatest transverse diameter was 14 cm. as compared with the diameter of the thorax, which was 26 cm.

Results of examination of the urine and of a complete blood count were normal. The basal metabolic rate was + 36 per cent. The value for cholesterol was 157 mg. per 100 c.c. of plasma.

In view of the evidences of congestive heart failure, the patient was confined to bed and 5 minims (0.31 c.c.) of strong solution of iodine (Lugol's solution) was administered three times daily. Administration of desiccated thyroid substance was discontinued. Auricular fibrillation continued for six days, at the end of which there was a return to normal rhythm. There was an associated abatement of the dyspnea, palpitation and tremor, and basal metabolism became normal. On the seventh day, however, auricular fibrillation reappeared and persisted for 12 hours; it was then replaced by a regular rhythm, with a pulse rate of 160 beats per minute. An electro-

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cardiogram was not made at this time, but auricular flutter was considered to be present.

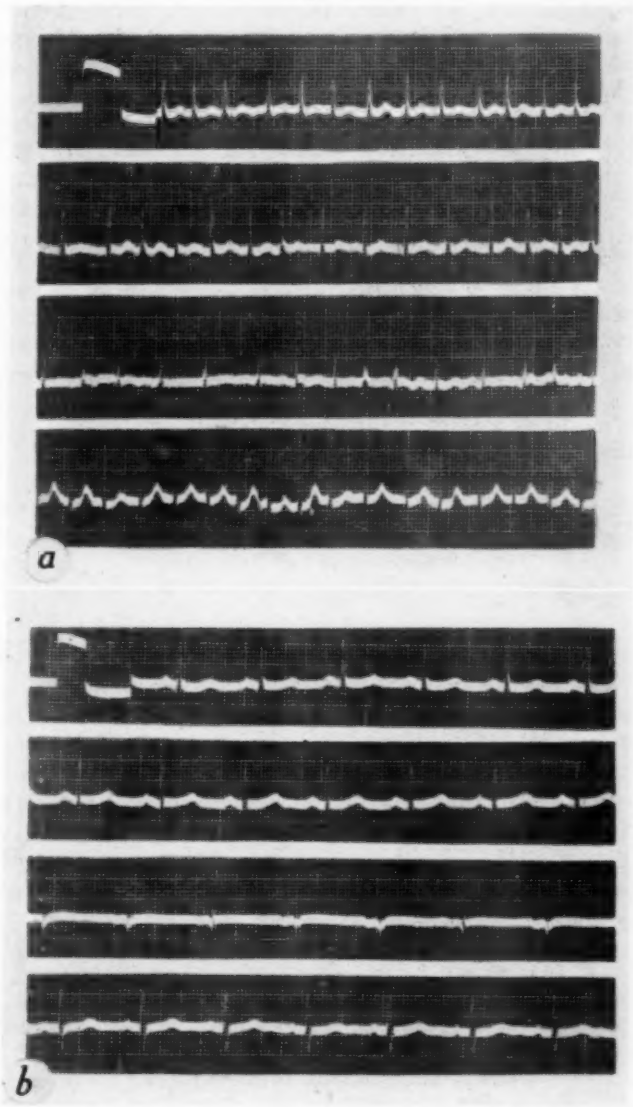

FIG. 1*a*. Auricular fibrillation occurring during the period of induced thyrotoxicosis in case 1; *b*, normal electrocardiogram after discontinuance of the taking of desiccated thyroid substance in case 1.

On December 6, 1940, eight days after the first examination of this patient, normal sinus rhythm again was present (figure 1*b*). The patient remained well through the day and complained of nothing. At 8:15 on the evening of the same day, the patient was examined: the pulse rate was regular, with a rate of 68 beats per minute;

the blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic; results of examination of the heart were normal. Five minutes later the patient was found unconscious, critically ill, with left hemiplegia. It was felt that she had suffered cerebral embolism secondary to intracardiac thrombosis and induced thyrotoxicosis.

During the next 24 hours the temperature of this patient increased to 101° F. (38.3° C.), and remained elevated for eight days. The pulse rate varied from 70 to 90 beats per minute, and it was always regular. The comatose state persisted for five days, as did complete left hemiplegia. The general condition of the patient gradually improved, and she was discharged from the hospital on January 1, 1941, 35 days after she had been admitted.

For the next three months there was gradual improvement in the condition of the patient, and at the end of this time some degree of function had returned to the left leg. Since then, and to the time of this report (a period of five years), the patient has been observed at frequent intervals. Results of all examinations of the heart have been normal. The pulse rate has been regular, varying from 68 to 80 beats per minute. Auricular fibrillation has not returned during this period, and repeated electrocardiograms have revealed normal sinus mechanism. The blood pressure has been normal, and there has been no recurrence of congestive heart failure. Orthopedic care has produced marked improvement in walking, but little improvement in the function of the patient's left arm has been noted.

In this case all the manifestations of thyrotoxic heart disease, including congestive heart failure, auricular fibrillation and probable cerebral embolism followed the ingestion of excessive amounts of desiccated thyroid substance over a period of one year. On the basis of the history of this patient, it appears that prior to the onset of congestive heart failure, auricular fibrillation and cerebral embolism, heart disease had not been present. In the five years subsequent to the episode of auricular fibrillation and cerebral embolism—at which time the taking of desiccated thyroid substance was discontinued—there has been no further evidence of heart disease. It seems probable that all the manifestations of heart disease in this case can be attributed to the use of desiccated thyroid substance in excessive amounts, because they appeared after prolonged use of this substance and disappeared after discontinuance of the use of the substance. Cerebral embolism probably arose from the development of mural thrombosis within the left side of the heart as a result of congestive heart failure and auricular fibrillation.

Case 2. The patient was a white female 60 years old, first examined on January 29, 1945. At that time the chief signs and symptoms were lightheadedness, vertigo and the sudden onset of irregular, rapid heart action. For several years this patient had been taking desiccated thyroid substance in doses of 2 to 3 grains (0.13 to 0.19 gm.), for myxedema. The dosage of desiccated thyroid substance had been increased by the patient to 7½ grains (0.49 gm.) taken daily, several weeks before I saw her. Slight dyspnea was present. The medical history was irrelevant. No evidence of thoracic pain in the past or present could be elicited.

The results of physical examination revealed an elderly white female who had moderate dyspnea and who manifested apprehension. The pulse rate was 140 beats per minute, and was grossly irregular. The temperature was 98° F. (36.6° C.) and the blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic. There was no demonstrable enlargement of the thyroid gland. Auricular fibrillation was present. A systolic murmur was heard over the pulmonic area. The lungs, abdomen and extremities were normal.

Results of examination of the urine and of the Kahn test were normal. The sedimentation time and blood count were within normal limits. The transverse diameter of the heart was 13.5 cm.; the transverse diameter of the thorax was 27 cm. There was no roentgenologic evidence of a substernal thyroid gland. An electrocardiogram revealed auricular fibrillation, with left bundle-branch block (figure 2*a*).

The patient was confined to bed and the administration of thyroid extract was discontinued. Strong solution of iodine (Lugol's solution) and digitalis were ad-

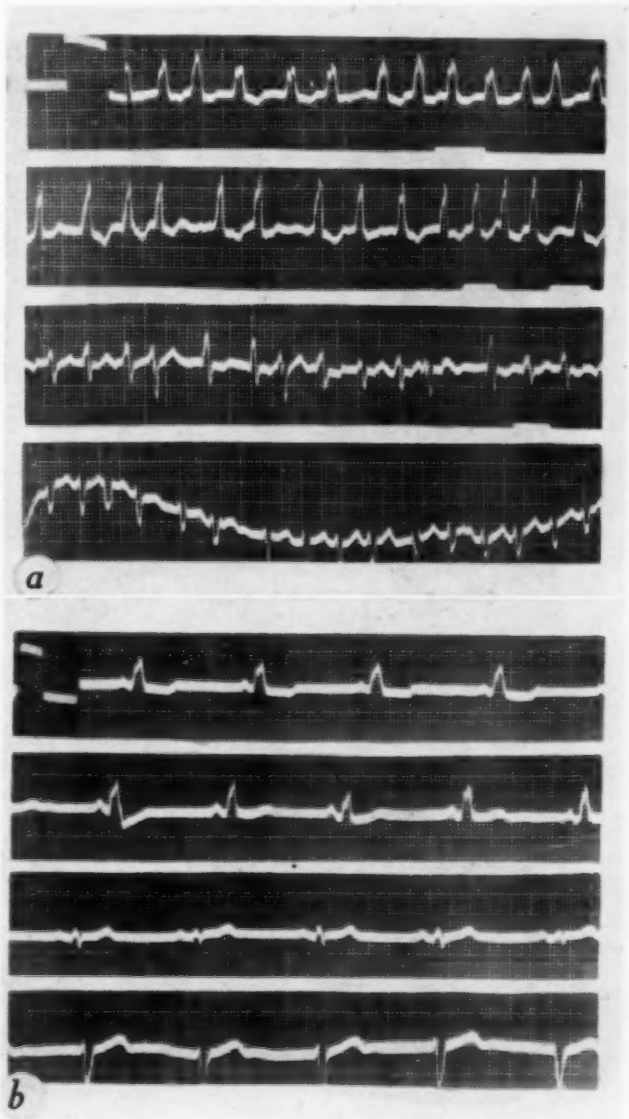

FIG. 2*a*. Auricular fibrillation and left bundle-branch block during the period of induced thyrotoxicosis in case 2; *b*, sinus mechanism and persistence of left bundle-branch block after discontinuance of the taking of desiccated thyroid substance in case 2.

ministered. Approximately 48 hours after the first examination of this patient, spontaneous resumption of normal sinus rhythm occurred. An electrocardiogram made one day later revealed sinus mechanism with persistence of left bundle-branch block (figure 2*b*).

During the next year this patient was observed at intervals. At no time subsequently was irregular heart action present, and to the time of this report there has been no dyspnea, pain in the thorax or palpitation. The pulse rate and blood pressure have been normal. After discontinuance of the taking of desiccated thyroid substance, evidence of myxedema associated with a basal metabolic rate of — 25 per cent appeared. The administration of desiccated thyroid substance in a dosage of 1 grain (0.06 gm.) daily was resumed without harmful effects.

In this case auricular fibrillation accompanied by dyspnea and palpitation was observed after the ingestion of excessive amounts of desiccated thyroid substance. These manifestations of thyrotoxic heart disease disappeared promptly after the administration of desiccated thyroid substance had been discontinued, and they have not reappeared to the time of this report. In this instance it is probable that the presence of bundle-branch block is evidence of coronary artery disease, and that an excessive amount of desiccated thyroid substance was sufficient to produce auricular fibrillation in a heart that exhibited evidence of previous disease. This is in contrast to the situation in the first case, in which no evidence of preëxisting or underlying heart disease could be demonstrated.

Comment

Two cases are presented in which the manifestations of thyrotoxic heart disease with auricular fibrillation were observed after the ingestion of large amounts of desiccated thyroid substance. In both cases discontinuance of the taking of desiccated thyroid substance resulted in prompt resumption of normal sinus rhythm. Hurxthal [1] has reported one case in which auricular fibrillation followed self-induced hyperthyroidism. Thyrotoxicosis may be the sole cause of heart failure,[2, 3] or the effect of thyrotoxicosis may be superimposed on organic heart disease of other causation, producing the manifestations of heart failure.[4, 5] In the first case reported herein the only demonstrable cause of congestive heart failure, auricular fibrillation, intracardiac thrombosis and cerebral embolization was thyrotoxicosis induced by the ingestion of desiccated thyroid substance. In the second case thyrotoxicosis was superimposed on coronary artery disease, with resulting auricular fibrillation.

It has been recorded that women tolerate thyrotoxicosis less well than men.[3] In both of the present two cases of induced thyrotoxicosis with cardiovascular manifestations the patients were women. Advancing age also favors the development of heart failure and auricular fibrillation in thyrotoxicosis.[4] The respective ages of the two patients reported on herein were 63 years and 60 years. Elderly people likewise are affected more readily than younger persons by thyroid extract, and when this extract is administered, it should be given with caution. It has been shown in this report that desiccated thyroid substance may, in the aged, produce the clinical manifestations of thyrotoxic heart disease without underlying heart disease, or the manifestations of thyrotoxic heart disease may, in turn, be superimposed upon coronary artery disease. Among elderly persons the manifestations of thyrotoxic heart disease in the absence of demonstrable thyroid enlargement should raise the question of induced hyperthyroidism.

SUMMARY

Two cases have been presented in which evidence of thyrotoxic heart disease appeared after the ingestion of excessive doses of desiccated thyroid substance. In the first case there was no preëxisting heart disease, and probable cerebral embolism and hemiplegia on the left occurred after a period of congestive heart failure with auricular fibrillation. The second case was complicated by coronary artery disease, and auricular fibrillation appeared for the first and only time after the ingestion of large amounts of desiccated thyroid substance. In both cases auricular fibrillation and other evidence of thyrotoxic heart disease disappeared promptly after discontinuance of the administration of desiccated substance.

CONCLUSIONS

Among older persons desiccated thyroid substance may produce the manifestations of thyrotoxic heart disease, including auricular fibrillation and embolism. The patient who presents evidence of thyrotoxic heart disease, in the absence of demonstrable goiter, should be questioned as to self-medication with desiccated thyroid substance.

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ACUTE FEBRILE ANEMIA AND THROMBOCYTOPENIC PURPURA WITH VASOTHROMBOSES *

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AN acute syndrome, characterized clinically by fever, anemia, thrombocytopenic purpura, renal, cardiac, and neurological manifestations, and pathologically by thrombotic lesions occluding arterioles, capillaries, and venules in almost every organ and tissue, was described by Baehr, Klemperer and Schifrin in 1936.[1] Moschcowitz [2] described a case with similar pathological finding but without purpura in 1925. To date only seven cases have been recorded in the

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literature, five from the Mt. Sinai Hospital in New York.[1, 2, 3, 4, 5] This number from one hospital suggests that the disease is a good deal more common than the literature would indicate, and that it is not being recognized elsewhere. For this reason we feel justified in reporting another case, in which the diagnosis was made before death. Further, although neurological manifestations have been prominent in all the cases reported, no neuropathological examinations have been reported. Complete examination of the central nervous system was available in this case.

Case Report

L. H., a 15 year old colored school girl, was admitted to the Cincinnati General Hospital on February 8, 1944, following the acute onset eight days earlier of sore throat, fever, headache, vomiting, hematuria and petechial eruption. The patient had enjoyed good health in the past except for frequent upper respiratory infections and for a single generalized convulsion at the age of 12. On January 31 she noted onset of nasal discharge, sore throat, some fever, and slight lower abdominal pain. On February 1, a physician prescribed sulfathiazole, 0.5 gm. every four hours, of which she took a total of 10 gm. There was no improvement and tender lymph nodes developed at the angles of the jaw. On February 6 she began to have more periumbilical and lower abdominal pain, and a second physician found tenderness in the right lower quadrant and gave more sulfathiazole (0.5 gm. every four hours for two days). She seemed to grow rapidly worse, developed headache, puffiness of the face, gross hematuria, red spots over face and chest, blurring of vision and delirium. On February 8 she became unconscious and was admitted to the Contagious Division.

Physical Examination: Temperature was 104.2° F.; pulse 136; respirations 32; blood pressure 120 mm. Hg systolic and 56 mm. diastolic. The patient was a well-developed and well-nourished colored girl, severely ill, unconscious, but responding to painful stimulation. Respirations were regular, deep and not embarrassed. The skin and mucous membranes were very pale, and scattered over the chest, abdomen and thighs were a moderate number of pin-head sized petechiae. There was slight periorbital edema and the conjunctivae were pale. The pupils were regular, equal, reacted promptly to light. Examination of the fundi revealed several large hemorrhages, some of which had white centers. The optic discs and retinal vessels were normal. The nasal mucous membranes were inflamed, and there was a mucopurulent discharge. The tongue was thickly coated. The buccal mucous membranes were pale, with several petechiae. The pharynx was slightly injected and some bloody phlegm was adherent to it. The neck was supple. The lungs were clear. The heart was not enlarged and no murmur was heard. The abdomen was flat, soft, and non-tender. Pelvic examination was not done (patient menstruating). All deep tendon reflexes were absent except for the ankle jerks.

Laboratory Data on Admission: Hemoglobin, 5.2 gm.; red blood cells, 1,490,000 per cu. mm.; white blood cells, 52,500 per cu. mm.; differential: Polymorphonuclear leukocytes, 84 per cent, basophiles, 1 per cent, lymphocytes, 13 per cent, monocytes, 2 per cent; there were 18 normoblasts per 100 white blood cells. The red blood cells revealed marked anisocytosis and poikilocytosis. There was no sickling of the red cells. A catheterized urine specimen had a specific gravity of 1.015, pH 5.5, albumin 4+; 3 to 4 white cells, 50 red cells, and a few granular casts per high power field. The blood urea mitrogen was 28 mg. per 100 c.c. A blood culture was negative. Agglutination for brucella was positive to a dilution of 1/320; Weil-Felix reaction was negative. The blood Wassermann reaction was negative. Lumbar puncture revealed an initial pressure of 220 mm. H_2O, final pressure of 150 mm. H_2O; the fluid was clear, contained 2 white blood cells per cu. mm., protein content was 32

mg./100 c.c.; sugar, 73 mg./100 c.c.; chloride, 726 mg./100 c.c.; Wassermann reaction, negative; culture, negative.

Teleoroentgenogram of Chest: Several calcifications were seen in either hilum. An irregular calcification about 1 cm. in diameter appeared in the right lower lung field. No definite area of infiltration was seen. The cardiac diameter was 14.5 cm. in a chest of 24 cm. diameter.

Course: Upon admission the patient was thought to be suffering from sepsis. Her course was stormy during the first week. The temperature ranged between 102 and 104° daily, pulse was compatible, and she was delirious. She was given sulfadiazine, 1 gm. every four hours, and on the third day this was changed to sulfamerazine. She also received five blood transfusions and intravenous glucose and saline. Several times she coughed up some bright red blood or blood tinged mucus, but examination of the lungs revealed no abnormalities. On the fifth day she was transferred to the medical service. At that time the physical examination was unchanged except that slight icterus was now noted and the icteric index was 12. The patient still appeared critically ill. Gallop rhythm was present. New petechiae continued to appear. Posterior cervical lymph nodes were enlarged and tender. Blood count on the third day was as follows: Red blood cells, 1,680,000 per cu. mm.; hemoglobin, 5.2 gm.; white blood cells, 33,250 per cu. mm.; differential, polymorphonuclear leukocytes 71 per cent, lymphocytes, 11 per cent, monocytes, 4 per cent, metamyelocytes, 9 per cent, "C" myelocytes 5 per cent, 43 normoblasts per 100 white blood cells. The red cells revealed marked anisocytosis, poikilocytosis, and microcytosis; reticulocytes were 11.6 per cent. The platelet count was 10,800 per cu. mm. The urine continued to show 2 + to 4 + albumin, red cells, white cells, casts, and the specific gravity was 1.012 to 1.015. At the end of a week, after a number of blood transfusions, the hemoglobin had risen to 8.0 gm./100 c.c.

An electrocardiogram on the sixth day revealed sinus rhythm, PR 0.19 sec., QRS 0.11 sec., all T-waves low voltage. Sulfamerazine was discontinued on the fifth day, and the blood level was 7.5 mg. per cent on the sixth day. During the subsequent two days the patient showed much improvement and by the ninth day temperature had fallen to normal. On the seventh day platelets had risen to 133,400, and white blood count had fallen to 12,650. A sternal aspiration revealed bone marrow that was hyperplastic for the erythroid series and megakaryocytes were present in normal numbers. No abnormal cells were seen. Petechiae disappeared, eyegrounds began to clear and mental status returned to normal. Gallop rhythm was still present when the patient sat up. Three electrocardiograms during the second week continued to show abnormalities (sinus tachycardia, PR 0.16–0.26 sec., QRS 0.10–0.12 sec., inverted T_1 and T_4, diphasic T_2, depressed ST_2). Icteric index fell to 6 and blood urea nitrogen to 13 mg. per cent. After the second week albuminuria was no longer found although occasional red cells, white cells and casts remained. Maximum specific gravity was 1.018. The hemoglobin rose to 10.5 gm., but the leukocyte count tended to be low (3,750 to 6,000) and an eosinophilia of 2 to 8 per cent was noted. An electrocardiogram just before discharge still showed prolonged auriculo-ventricular and intraventricular conduction, and low voltage T-waves, but the rate was 60. A teleoroentgenogram of chest on the eighteenth day revealed that the heart measured 12.5 cm. in a chest of 25.5 cm.

The reaction to the various sulfonamides was tested. On the thirteenth day 0.5 gm. sulfathiazole (orally) was followed in four hours by chill, malaise, rise in temperature to 104.2° F, tachycardia (140), confusion, leukocytosis (19,150 per cu. mm.), but no change in hemoglobin, red blood cell count, urine, or icteric index. The reaction cleared entirely in 24 hours. On the eighteenth day 0.5 gm. sulfadiazine was given and resulted in an almost identical reaction (temperature 104.8° F., pulse 140, white blood count 18,000 per cu. mm.) There was no reaction to sulfanilamide (up

to 2 gm.) and a very mild reaction to sulfamerazine. Patch tests with the four sulfonamides were negative. The patient was discharged on the forty-second hospital day, March 21, 1944, 50 days after the onset of her illness.

During the subsequent month the patient was followed in the out-patient department. Subjectively she felt well except for palpitation and some dyspnea. Examination revealed tachycardia but no cardiac murmurs. However, urine always revealed + to ++ albumin, and a few leukocytes and red cells and casts; specific gravity ranged from 1.018 to 1.023. An anemia persisted (red blood count 3.00—3.80 mil. per cu. mm.) and the leukocyte count ranged between 4,600 and 8,000 per cu. mm. On one occasion eosinophilia of 8 per cent was present. An electrocardiogram on March 28, 1944 revealed T_3 inverted, PR 0.16 sec. and on April 18, 1944 PR 0.24 sec. and low voltage T-waves in all leads. The patient received ferrous sulfate as the only medication. On April 25, 1944 the patient noted a sore throat, malaise and fever and a petechial eruption developed. Menstrual bleeding began. She did not improve and two days later was admitted to the hospital.

Physical Examination: Temperature was 100° F., pulse 110, respirations 20, blood pressure 112 mm. Hg systolic and 70 mm. diastolic. The patient appeared moderately ill, drowsy, pale, and numerous fresh petechiae were noted over the chest, abdomen, back, extremities, conjunctivae and buccal mucous membranes. Enlarged lymph nodes were felt in the neck and axillae. Examination of the optic fundi revealed several old and recent hemorrhages, but normal retinal vessels. A small superficial necrotic area with dirty gray membrane was noted over the right tonsil and a large hemorrhage was found over the anterior tonsillar fold. The lungs were clear. The heart was enlarged, gallop rhythm was present and a rolling systolic murmur was heard over the base, transmitted to the neck and toward the apex. The second pulmonic sound was louder than the second aortic sound. The abdomen was soft, not tender, and no organs were felt. The deep reflexes were depressed, but no pathological reflexes were elicited. The patient's course was stormy. The temperature gradually rose and by the fourth day was ranging between 102 and 104° F. She received several blood transfusions. Skin purpura, retinal hemorrhages and vaginal bleeding increased, and on the sixth day liver and spleen were noted to be palpable 1 to 2 cm. below the costal margin. She lapsed into coma and the head and eyes were noted to be turned to the right, with spontaneous lateral nystagmus. The right pupil was 6 mm. in diameter and the left pupil 4 mm., and both reacted poorly to light. There was a left central facial weakness, the left arm was spastic and the left leg paretic and flaccid. Plantar reversal signs were elicited on the left. No platelets were observed on the stained blood smear that day. An emergency splenectomy was performed that night. The temperature rose to 106° F. On the next day a right facial weakness was noted, both pupils were dilated and non-reactive and both legs were flaccid and paralyzed. Hemorrhages occluded both optic discs. The patient went into shock and died the following day.

Laboratory Data: Hemoglobin, 6.0 to 8.0 gm. per 100 c.c.; red blood cells, 1,550,000 to 2,870,000 per cu. mm.; white blood cells, 10,000 to 48,000 per cu. mm.; differential, polymorphonuclear leukocytes 60 per cent, eosinophiles 2 per cent, lymphocytes, 30 per cent, stab cells 8 per cent; reticulocytes, 3.8 per cent; platelets, 110,000 per cu. mm. There was no sickling of the red blood cells. The bleeding time was 11 minutes, and the clotting time 7 minutes. The fragility test showed a range of 0.26 to 0.38 (normal 0.32 to 0.48). Urine: specific gravity, 1.005 to 1.020; albumin 3+, occasional red cells, white cells and casts. The blood urea nitrogen was 9 mg. per 100 c.c.; icteric index, 16, protein, 6.16 gm. per 100 c.c.; the van den Bergh reaction was moderately positive, prompt diphasic. The Weil-Felix reaction and heterophile agglutination were negative. Urine and blood cultures were negative. A bone mar-

row biopsy revealed hyperplasia in the red cell series with increase in early erythroblasts, while the myeloid elements and megakaryocytes were normal.

An electrocardiogram revealed sinus tachycardia, rate 110; PR interval 0.16 sec.; QRS 0.08 sec.; all T-waves inverted and $ST_{2 \text{ and } 3}$ depressed.

Necropsy Findings: The necropsy was performed 19 hours post mortem. The body, measuring 162 cm. in length, was that of a well developed and nourished negro

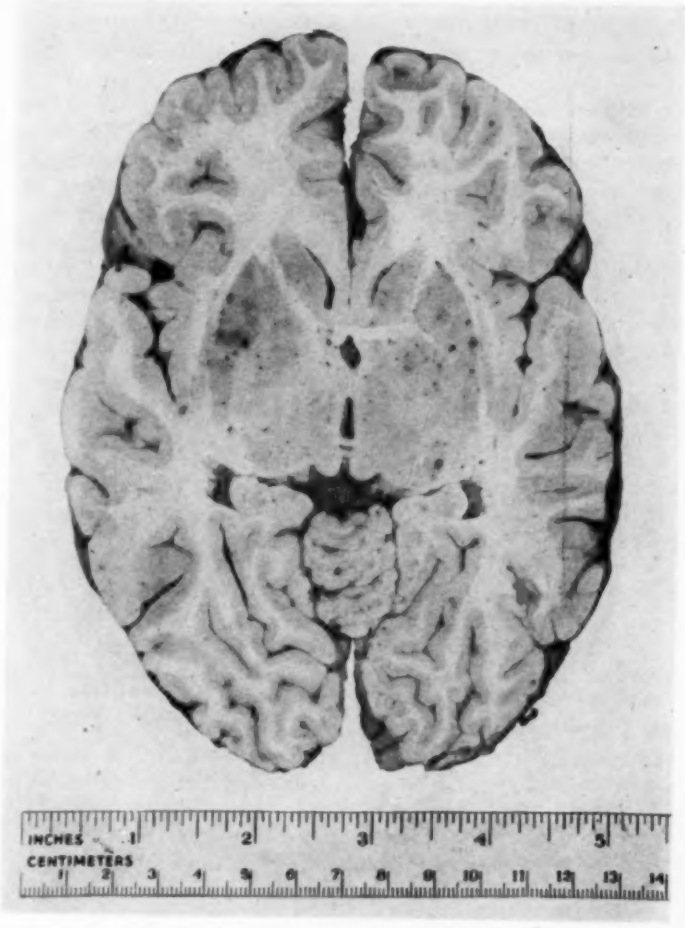

FIG. 1. Horizontal cut through the brain. Note the scattered petechial hemorrhages in the basal ganglia on the left and in the folia of the cerebellum.

girl. Numerous inconspicuous petechiae and purpuric areas were distributed widely over the body. There was an unhealed upper left rectus incision wound measuring 8 cm. in length.

The usual "crutch" incision revealed the absence of the spleen, several black silk sutures in the splenic pedicle, and friable fibrinous adhesions binding the omentum to the pedicle. The peritoneal surface of the left dome of the diaphragm and the serosa of the stomach, small and large intestines presented numerous petechiae. Elsewhere the peritoneum was normally thin, smooth, and translucent. The panniculus was

moderately thick, and the musculature well developed. The remaining viscera of the abdomen were in their usual relations. The slightly enlarged mesenteric and periaortic lymph nodes were uniformly firm and light red. The peritoneal cavity contained about 500 c.c. of clear yellow serous fluid. The adult female breasts presented no masses. Removal of the normal breast plate revealed the organs of the thorax in their usual relations. The pleural surfaces over both lungs were normally thin, smooth, and translucent. Each pleural space contained about 500 c.c. of clear yellow serous fluid. The pericardial sac was normally thin and pliable, contained about 400 c.c. of clear yellow serous fluid, and measured 17 cm. in greatest transverse diameter. The chest was 27 cm. wide. The structures of the neck were not examined.

The heart weighed 320 grams and was flabby. The light tan and brown mottling of the myocardium was visible through the normally thin, smooth and translucent epicardium and mural endocardium. The cut surfaces of the myocardium also showed numerous petechiae. The right atrium was dilated. Along the line of closure of each mitral valve leaflet was a row of several red, soft, friable verrucous vegetations measuring up to 2 mm. in diameter. The remainder of the mitral valve leaflets, the chordae tendineae, and the other valves appeared normal. The thin walled, patent coronary arteries showed a few scattered smooth, soft, slightly elevated, yellow, intimal plaques. The aorta and its branches showed no regions of dilatation or narrowing, and the intima of the aorta showed a few scattered, soft, yellow plaques.

The lungs appeared normal in size. The upper lobes of both lungs were mottled light and dark gray, crepitant, soft and elastic. The cut surfaces of these lobes were grayish-pink and relatively dry. The lower lobes of both lungs were dark blue, firm, subcrepitant, and inelastic, and the cut surfaces evenly dark red and dry. The smooth, unbroken mucosa lining the patent bronchi was uniformly reddened. The hilic lymph nodes were slightly enlarged. The liver weighed 1,740 grams. The cut surfaces of the reddish-brown substance were inconspicuously mottled with numerous small dark red areas. The gall-bladder was thin-walled and contained liquid bile, and the bile passages were patent. The pancreas externally appeared normal, and on section showed the usual lobular arrangement of the evenly tan substance. The mucosa of the esophagus and stomach showed the usual postmortem changes. The smooth and unbroken mucosa of the small and large intestines presented focal regions of congestion.

The kidneys were similar in size and together weighed 365 grams. The thin capsules stripped easily, and there were several small stellate depressed regions. Both the external and cut surfaces presented many bright red round dots measuring less than 1 mm. in diameter. The cortices were of uniform width and were poorly demarcated from the light brown pyramids which showed numerous thin linear glistening white markings radiating from the apices to the bases. On the cut surface of one kidney there was a single triangular firm grayish-yellow area with its base at the cortex and apex at the pyramidal border. The smooth unbroken mucosa of the pelves was slightly elevated and markedly reddened in scattered, small, rounded regions. The ureters appeared normal. The mucosa of the urinary bladder was reddened.

The ovaries, uterus and cervix appeared grossly normal. The suprarenal glands externally appeared normal. On the cut surface there were small, poorly demarcated, red areas distributed through the usual thin peripheral band of orange cortex. The medullae were normally firm and gray. The hypophysis appeared normal.

Microscopic Examination: Sections of the viscera revealed partial or complete occlusion of the small blood vessels (arterioles, capillaries, and possibly venules) by rounded plugs of finely granular material which stained brightly with eosin. The diameters of the affected vessels were increased. The plugs were attached to the walls

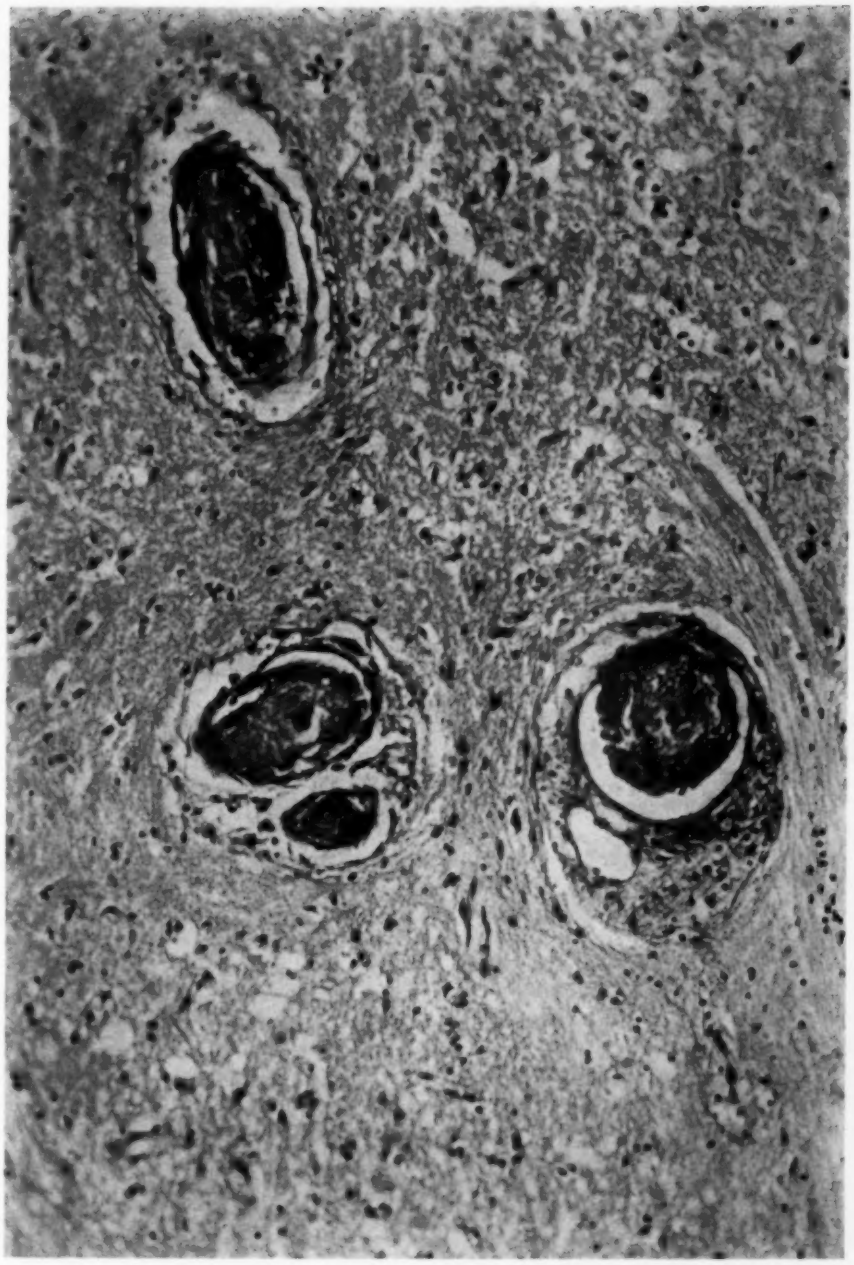

FIG. 2. Thrombotic occlusion of a large number of smaller blood vessels (veins and capillaries) of the basal ganglia. Hematoxylin eosin stain × 185.

of the vessels along a portion of their margins. In the substance of a few of the plugs were red blood cells and nuclear debris. The endothelial cells lining these vessels were swollen and showed evidence of proliferation. Many of the plugs were partially covered with endothelium. The walls of the vessels adjacent to the site of attachment of the plugs showed degenerative changes, and in a few vessels frank necrosis. There was little inflammatory reaction in or around these vessels. Varying stages of organization of the plugs were present in a given organ, and rarely in a single vessel. These changes in the smaller vessels were particularly prominent in the sections of heart, kidneys, and adrenals, but were also present in sections of the pancreas, liver, gall-bladder, gastro-enteric tract, lungs, urinary bladder, uterus, and lymph nodes. The larger arteries and veins appeared normal.

In the heart, the vascular lesions were distributed throughout the myocardium, which in addition showed scattered miliary areas of necrosis and polynuclear leukocytic infiltration, and also regions composed of broad bands of fibrous connective tissue and small island of myocardial fibers. One auricular appendage contained a thrombus. There were bacteria-free thrombotic vegetations on the mitral valve leaflet and the subjacent tissue of the valve showed no inflammatory reaction. Several subepicardial petechiae were present.

The vascular lesions in the kidneys were more frequent in the cortices and involved the arterioles and glomerular capillaries. The basement membrane of all the glomeruli throughout the kidneys was invariably slightly thickened. Frequent subcapsular triangular regions of atrophic tubules and increased interstitial tissue infiltrated with round cells were present. There was a single ischemic cortical infarct. The tubular epithelium showed marked cloudy swelling.

In the liver the vascular lesions were found in the small vessels of the capsule and the branches of the hepatic artery in the portal spaces. There was also congestion of the sinusoids with central zone atrophy of the liver cords. The vascular lesions in the adrenals were most frequent in the subcapsular portion of the cortex. Numerous small extracapsular hemorrhages were present.

In the lungs the vascular lesions were distributed throughout the framework. There was also congestion and edema, and a single small focal area of necrosis and hemorrhage.

There was diffuse lymphocytic infiltration of the slightly increased interstitial tissue of the pancreas. The lymph nodes were congested. The vascular lesions were the only departure from normal in the gastro-enteric tract, the gall-bladder, and the uterus. The wall of the urinary bladder showed an acute inflammatory reaction with superficial ulceration of the mucosa.

Neuropathological Examination: The gross examination of the brain revealed multiple minute areas of softening diffusely scattered throughout the gray matter of both hemispheres. The largest lesion was found in the left occipital lobe (Area 19), measuring 1 cm. in mesio-lateral extent and 5 mm. in anteroposterior direction. The significant findings seen on horizontal cuts through the brain are illustrated in figure 1. Diffusely scattered petechial hemorrhages measuring about 1 mm. in diameter were seen in the basal ganglia on the left, in the folia of the cerebellum and in some areas of the cortical ribbon. The balance of the ventricular system appeared normal.

Survey sections were taken from several areas of the gray and white substance of both hemispheres and stained with hematoxylin-eosin, Cresyl violet, H. v. Gieson, phosphotungstic acid hematoxylin, Giemsa, and by the Loyez myelin sheath and Bodian 1 per cent protargol silver methods.

The histologic examination disclosed: (1) vascular lesions and (2) alterations of the nervous tissue proper.

(1) The vascular lesions were characterized by thrombotic occlusion of a large number of smaller blood vessels, chiefly, involving the capillaries and venules of the

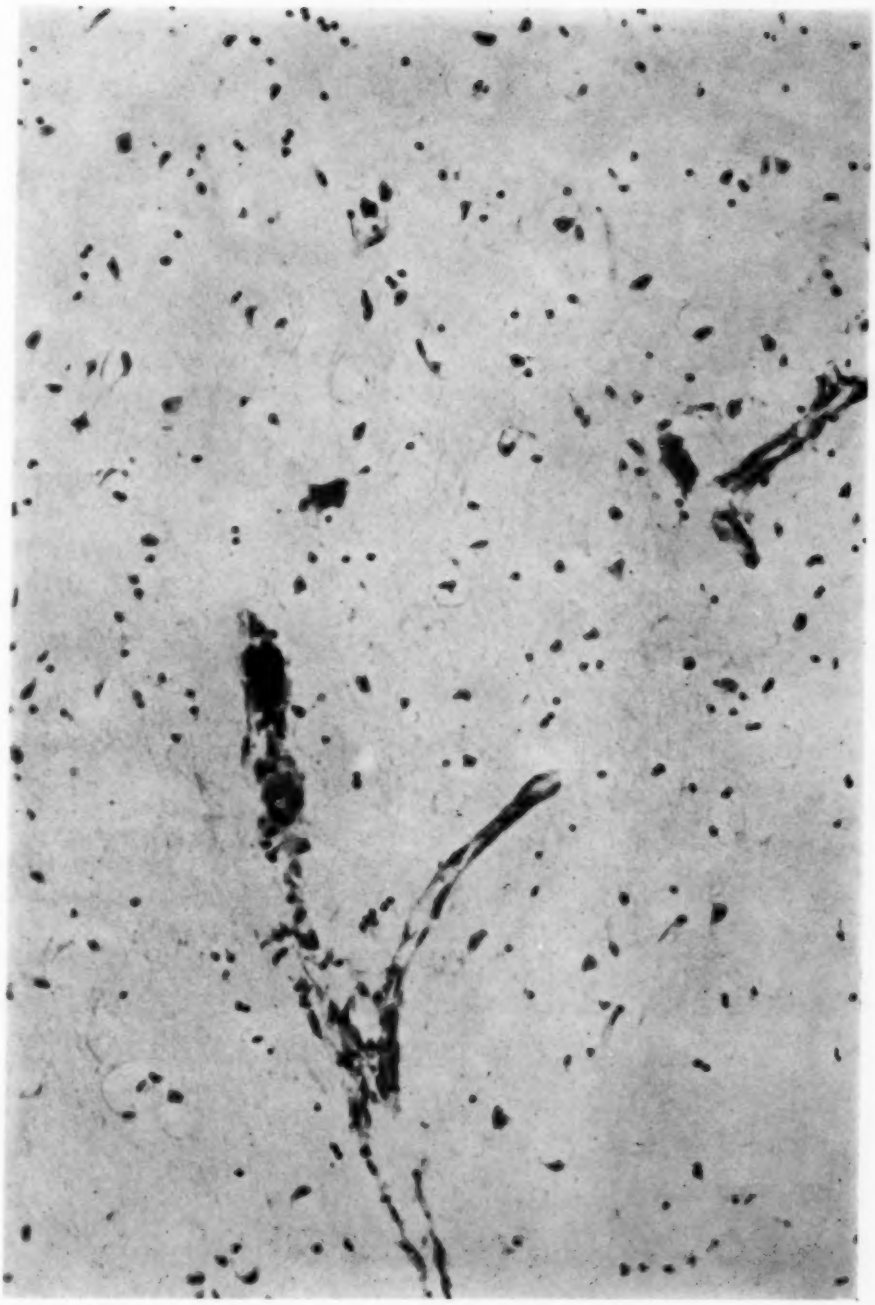

FIG. 3. Hypertrophy and proliferation of the endothelial cells of the partially thrombosed capillaries. Cresyl violet stain; × 220.

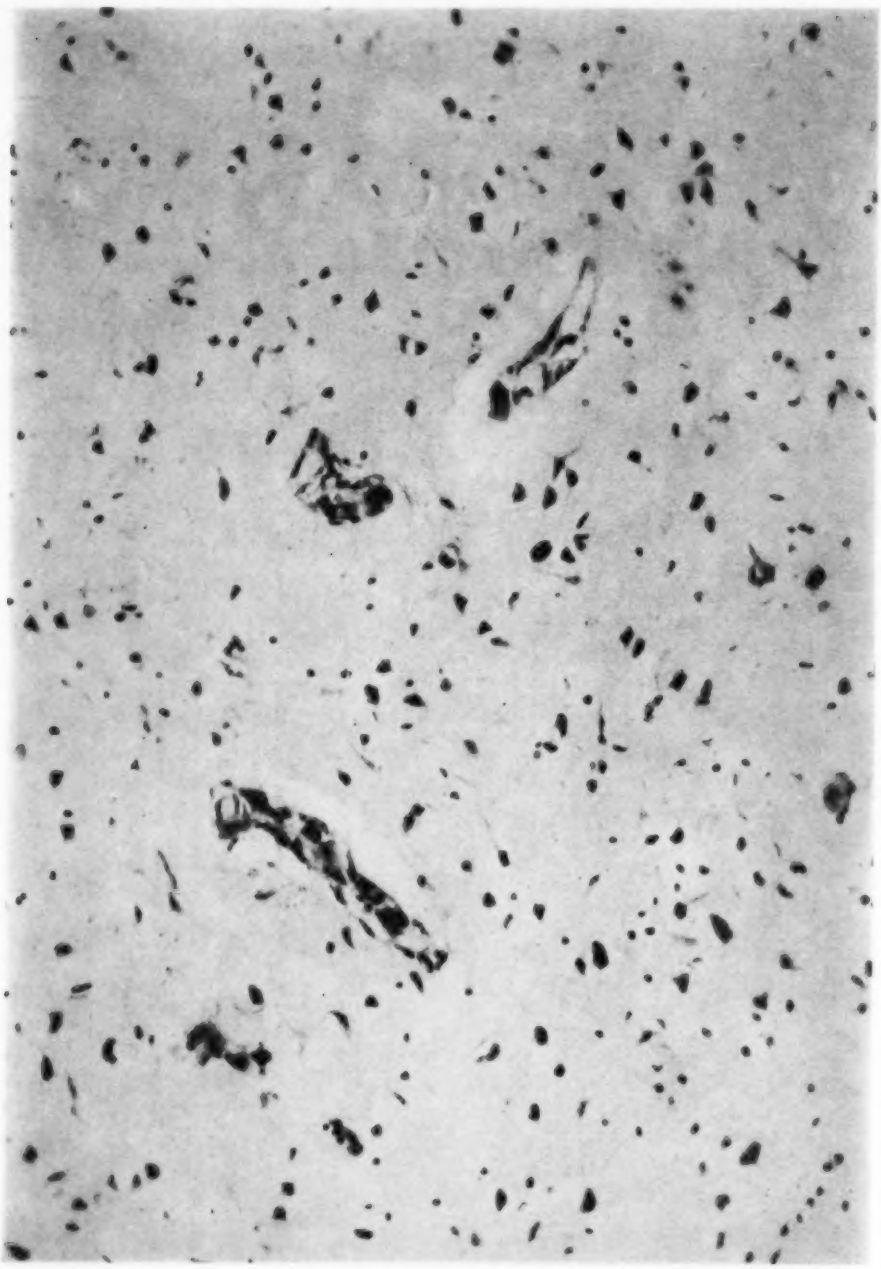

FIG. 4. Hypertrophy and proliferation of the endothelial cells of the capillaries in absence of thrombotic occlusion. Cresyl violet stain; × 260.

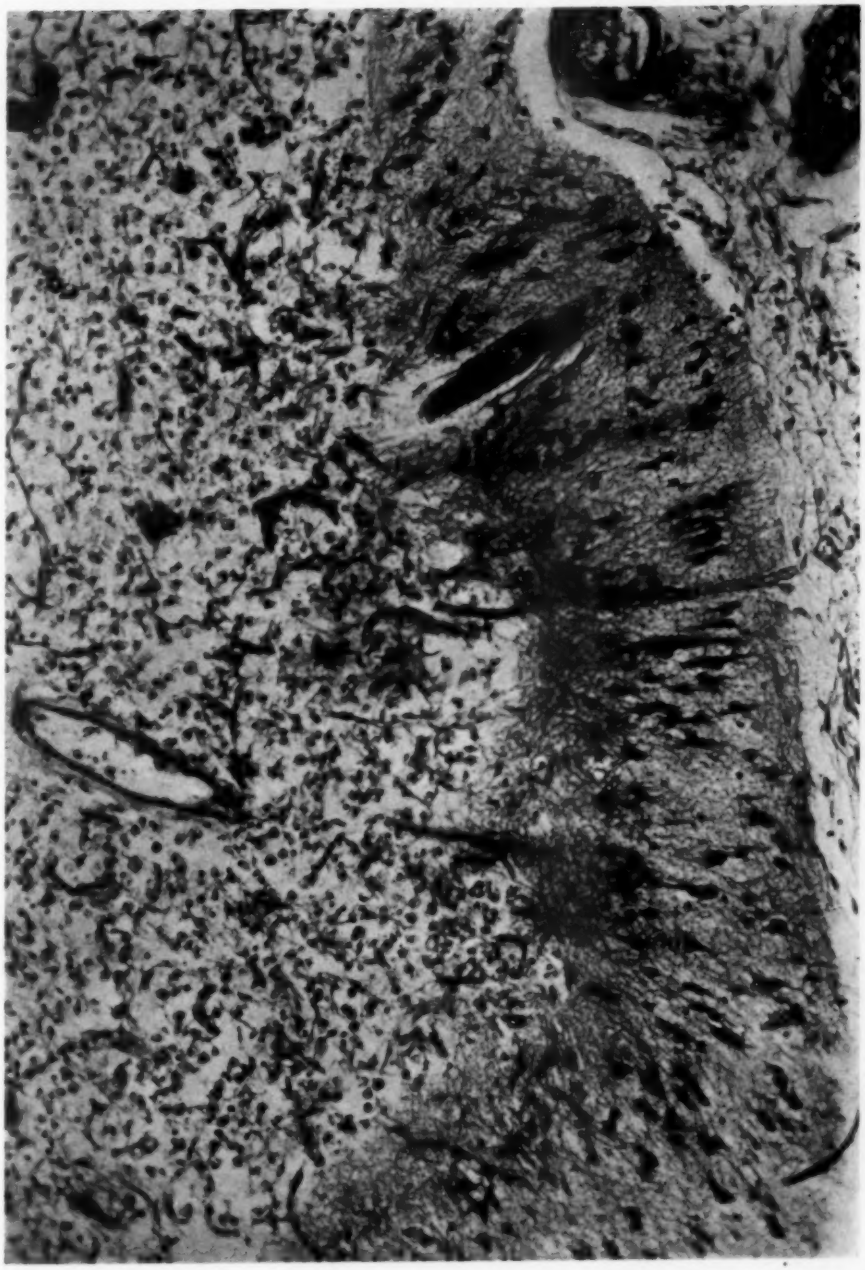

FIG. 5. Focal area of softening with large accumulation of gitter cells surrounded by an area of gliosis. Hematoxylin eosin stain; × 135.

cortical gray matter and basal ganglia. The affected blood vessels appeared distended, their lumina were completely or partially occluded by a homogeneous or slightly granular thrombotic mass stained pinkish with hematoxylin eosin (figure 2). On closer examination it appeared that the thrombi contained only a small amount of white blood cells and very few fibrin threads. In preparations stained with Giemsa stain no platelets could be identified. The large majority of the thrombi seemed to be composed of large masses of granular debris. In sections stained with hematoxylin van Gieson the thrombotic masses were stained yellow. By means of special stains for fibrin (phosphotungstic acid hematoxylin) it was possible to demonstrate that the thrombi contained very little fibrin. Of note were the changes seen in the vessel wall. These lesions were characterized by a marked proliferation and swelling of the lining endothelium (figure 3). In some of the occluded blood vessels there were to be seen definite signs of organization of the thrombi; they appeared invaded by numerous endothelial cells and fibroblasts and were adherent to the vessel wall. In less advanced lesions the thrombi appeared only slightly attached to the vessel wall. Occasionally the lining endothelial cells showed very mild degenerative lesions and no proliferative changes. Finally, there were recent lesions in which the vessel wall of the occluded capillaries and veins appeared generally well preserved or showed only a minimal degree of endothelial proliferation. It is of interest that some of the capillaries in which there was no evidence of occlusion showed a moderate degree of proliferative and degenerative alterations of the endothelial cells (figure 4). There were no signs of an inflammatory process and no necrotic lesions of the subendothelial connective tissue present. The larger blood vessels did not disclose any pathologic changes; their lining endothelium appeared fairly well preserved.

(2) Changes in the nervous tissue proper, secondary to the circulatory disturbances, consisted of disseminated small foci of softening, characterized by a large accumulation of fat granule cells. In some of the older lesions confined to the cortical ribbon there was to be seen a layer of dense glial reaction especially marked in the overlying molecular zone of the cortex (figure 5); this contained numerous hypertrophied glial cells, mostly astrocytes with large protoplasmatic bodies and numerous processes. In many instances the small focal lesions showed more recent alterations in the form of a tissue rarefaction or early signs of anemic infarction (figure 6). And finally there were numerous scattered cortical lesions in which only a small number of nerve cells appeared degenerated and destroyed. Between these earliest lesions and those associated with glial scar formation, there were numerous transitional stages. In addition there was a small number of diffusely scattered small hemorrhages present. The leptomeninges appeared normal. No signs of an inflammatory process could be detected.

Anatomical Diagnoses: Acute degenerative vascular disease with thrombosis involving the small vessels, widely distributed throughout the viscera and brain; non-bacterial thrombotic mitral valvulitis; renal, pulmonary, and miliary myocardial and cerebral infarcts; myocardial fibrosis; petechial hemorrhages in the skin, pericardium, peritoneum, and renal pelves; pulmonary congestion and edema; chronic passive congestion of the liver; bilateral hydrothorax; hydropericardium; ascites; acute cystitis; slight interstitial fibrosis of the pancreas.

Discussion

The postmortem examination in this case leaves little doubt that it represents an example of the condition described originally by Moschcowitz [2] and by Baehr, Klemperer, and Schifrin.[1] Clinically, the patient, a young girl, presented fever, thrombocytopenic purpura, hemolytic anemia, and evidence of involvement of kidneys, heart and the central nervous system. The onset was acute, following

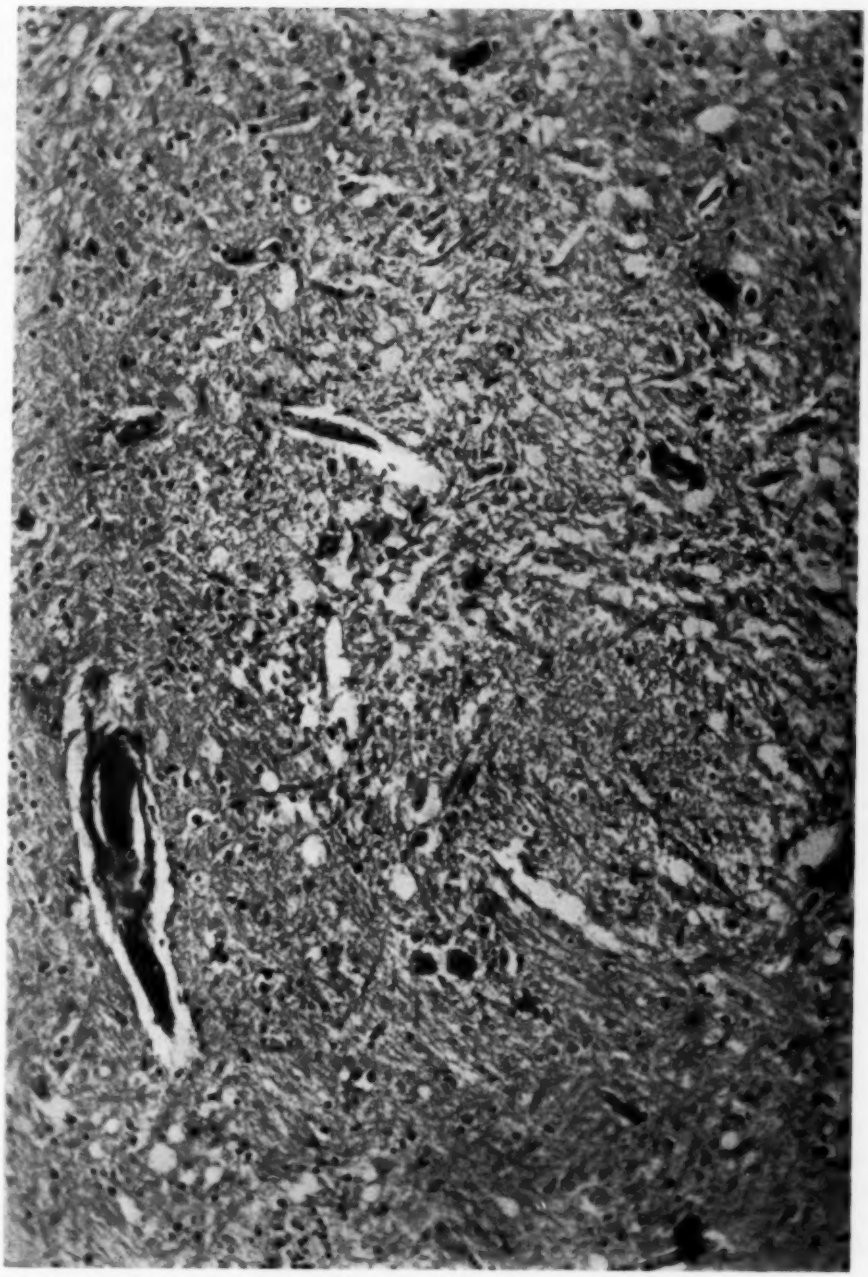

FIG. 6. Small area of recent softening characterized by tissue rarefaction and necrosis. Hematoxylin eosin; × 160.

what may have been an upper respiratory infection, the course stormy for the first week and then followed by improvement, permitting discharge from the hospital after a six weeks' stay. However, she obviously never recovered, for in the interval between admissions she continued to have weakness, anemia, and evidences of renal and myocardial involvement. On the first admission the possibility that the illness represented a hypersensitivity to sulfonamides was considered and indeed such a sensitivity was demonstrated. However, although the patient improved after the sulfonamides were discontinued, she continued to have signs of active disease and the final exacerbation occurred without the patient having received any sulfonamide. The presence of renal, myocardial, and nervous system involvement along with the fever, thrombocytopenic purpura, and anemia suggested that this case did not fall into the usual group of thrombocytopenic purpura and the correct diagnosis was suggested. The splenectomy was obviously ill-advised, since splenectomy has not proved helpful in any of the cases reported in the literature.

The pathological findings were typical and except for the findings in the central nervous system revealed little that has not been well described in the literature. However, this patient survived longer than any of the other patients reported. For this reason many lesions showed a greater degree of organization than usual, as evidenced by the areas of fibrosis in the myocardium, the thickening of the basement membrane of glomeruli, and the dense glial reaction in the brain. In general, also, there seemed to be a greater degree of endothelial proliferation and of vessel wall change than is described in the other cases. These, too, may represent old lesions. In some instances the thrombotic plugs were covered with endothelium.

The widespread distribution of small blood vessel occlusions in the brain explains the frequency and character of the neurological manifestations of this disease. Evidence of multiple focal involvement of the brain has been the usual clinical finding. It is clear from our observations that healing with gliosis may take place.

The involvement of the heart was very extensive in this case and clinically was manifest by enlargement, gallop rhythm, dyspnea, and by persistent electrocardiographic abnormalities. The widespread distribution of areas of miliary necrosis and fibrosis indicate old and recent damage due to small vessel occlusion. Thrombotic non-bacterial endocarditis was also present in this case. Although this type of endocarditis does not usually give any physical findings, this patient developed a rather prominent murmur between her first and second admissions. This cannot be accounted for on the basis of anemia, which was severe on both admissions. In all likelihood the renal infarct and possibly the white centered fundal hemorrhages represented embolic phenomena arising from these vegetations.

We have no suggestions as to the etiology of this condition. The development of an exacerbation after what may have been an upper respiratory infection suggests some type of unusual response to infection. The patient did manifest sensitivity to sulfonamides, which may cause febrile reactions, thrombocytopenia, and hemolytic anemia, but there was no evidence that these drugs played any etiologic rôle in this case. Of the cases reported in the literature acute infection has not been a prominent preceding event. One of the cases had a sibling

who had thrombocytopenic purpura and another had a sibling who died of periarteritis nodosa.[1]

There is no clinical or pathological evidence at this time to suggest a relationship between this condition and Libman-Sacks disease (disseminated lupus erythematosus) in spite of the prevailing occurrence of both diseases in young women. According to Klemperer there are several unreported cases of febrile thrombocytopenic purpura among males.[6] Clinically Libman-Sacks disease is characterized by a more chronic and remitting course, and may include pleurisy, pericarditis, joint involvement, skin lesions, a typical verrucous endocarditis, lymph node involvement, pneumonitis, and myositis, none of which is a feature of febrile thrombocytopenic purpura. Thrombocytopenia may occur in Libman-Sacks syndrome but purpura and hemorrhagic phenomena are not presenting symptoms in that disease. Pathologically the two diseases show few similarities. The pathologic findings of Libman-Sacks disease, that is, the "wire-loop" glomerular lesions, the verrucous endocarditis, the perivascular sclerosis in the spleen, the pericardial lesions (signet-cell lesions, "hematoxylin staining bodies," the eosinophilic multinuclear coalescent bodies, and endothelial bud capillaries), and the evidences of collagen involvement,[7] are not seen in the acute febrile thrombocytopenic purpura. Conversely the widespread hyaline thrombotic lesions noted in this case are not a feature of Libman-Sacks disease, although occasionally thrombotic lesions are found.

Summary

The case of a young woman with acute onset of fever, purpura, thrombocytopenia, hemolytic anemia, and evidences of renal, cardiac, and central nervous system involvement is presented. Postmortem examination revealed widespread thrombotic lesions involving arterioles, capillaries, and venules of the brain and all the viscera. The identity of this disease with that described by Moschcowitz and by Baehr, Klemperer, and Schifrin is pointed out and the clinical and pathological features are discussed.

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ENCEPHALOMYELORADICULITIS (GUILLAIN-BARRÉ SYNDROME) AS A COMPLICATION OF INFECTIOUS HEPATITIS *

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DYSFUNCTION of the central nervous system has been described as one of the more serious complications of infectious hepatitis.[1, 2] Ordinarily the picture resembles acute alcoholism, hyperinsulinism or anoxia of the brain and is said to indicate a grave prognosis.[3] Symptoms suggestive of involvement of the basal ganglia have also been noted,[4] but no record of myelitis, radiculitis or neuritis appearing in a patient with acute hepatitis was found in a survey of the recent literature.

In 1916 a symptom complex, characterized by clinical evidence of radiculitis and "acellular hyperalbuminosis" in the spinal fluid was first described.[5] The name Guillain-Barré syndrome has been most commonly used to designate this picture. It has also been called infective polyneuritis, radiculitis, myeloradiculitis and "myelitis of obscure origin." When the brain stem or cerebral hemispheres are involved, the condition has been referred to as encephalomyeloradiculitis.

Grinker [6] states that "this syndrome of nerve, root and cord disturbance occurring separately or combined, is an acutely appearing condition arising during the course of or after a systemic infection, usually of the upper respiratory tract." Frequently there are only mild transient disturbances of motor power and sensation preceded or accompanied by root pains. On the other hand, complete paraplegia and quadraplegia may occur and with involvement of the brain stem and subsequent respiratory paralysis, death may ensue. The paralysis is of the lower motor neurone type, the sensory involvement is usually radicular in type with ill-defined "glove" and "stocking" distribution.

The syndrome attains a certain severity, remains stationary for some days, then begins to recede gradually, often over a period of many months. Deaths are not infrequent in adults, but rare in children. If death does not occur at the height of the disease, recovery is usually complete. Thus the diagnostic features of the disease are a transient myeloradiculitis with increase in the protein level but little or no change in the cell count of the spinal fluid.

The following case is described because of the uniqueness of this neurological syndrome appearing as a complication of acute hepatitis. Of further interest was the presence of an anatomical anomaly which was at first thought to explain the early neurological signs and symptoms.

CASE REPORT

A 25 year old paratrooper sergeant was admitted to the hospital on March 20, 1945 complaining of malaise, anorexia and epigastric pain. Two days prior to entry his urine became dark and on the following day he noted jaundice. Past history was significant in that he had been ill for four weeks in 1939 with "catarrhal jaundice."

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Recovery from the previous episode of jaundice had apparently been complete, and the patient had been well since that time. Alcohol ingestion consisted of occasional moderate indulgence in beer. He had never received yellow fever vaccine.

On admission the temperature was 98.4° F., pulse 68, respirations 16. Skin and sclerae were moderately icteric. There was generalized adenopathy. The liver was 2 cm. below the right costal margin and moderately tender.

Laboratory studies showed a hemoglobin of 14.6 mg., 4.7 million red cells and 6,400 white cells per cubic mm. of blood. The urine was normal save for the presence of 12.6 mg. of urobilinogen and "two plus" bile. Icterus index was 44 and the sedimentation rate 8 mm. in one hour.

On a regimen of complete bed rest and a high protein, low fat diet, the patient showed gradual recession of the icterus and other signs and symptoms. After three weeks, the icteric index was normal and all signs of disease, save for persistent slight enlargement and tenderness of the liver and occasional temperature elevation above 99° F. had disappeared. On April 10 he began to complain of pain and numbness in the finger tips bilaterally. Supraclavicular pressure and turning of the head to the opposite side accentuated the symptoms. A roentgenographic examination of the cervical spine showed bilateral cervical ribs and it was assumed that the symptoms were due to this. During the following few days, however, pain in the calf muscles and upper back appeared. On April 16 neurological examination revealed marked hypesthesia of all modalities of the "stocking type" bilaterally to the knee, and of the "glove type" to the wrist on the right and "gauntlet type" to the elbow on the left. The patellar, achilles, bicipital, and tricipital reflexes were absent. The abdominal and cremasteric reflexes on the left were present, but exhaustible on the right. Cranial nerves at this time showed no abnormalities. On the following day the left and right lower abdominal reflexes were absent but the right upper present. On that day a left facial weakness of the lower motor neurone type was noted, and a flaccid paralysis of both arms and legs appeared. Lumbar puncture on April 17 revealed the fluid to be clear and under 200 mm. pressure. There were present 70 mg. of protein per 100 c.c. and only 4 cells (all lymphocytes) per c.c. of spinal fluid.

There was no further change in physical status for the following week, but on April 27, 1945, spinal fluid contained 192 mg. of proteins per 100 c.c. and 6 cells (lymphocytes) per c.c. of spinal fluid. At that time the facial weakness began to recede, and a slight return of muscle function in the arms was noted. Therapy consisting of passive motion and massage was instituted, and very slow but progressive return of muscle function occurred during the following month. On May 20 he was evacuated to the United States. At that time deep reflexes and voluntary contractions of all muscle groups in the arms were present, but were still absent in the lower extremities. A letter received from the patient in August 1945 stated that he was walking normally and that he had full use of his arms and legs.

Comment

The neurological and laboratory features, as well as the clinical course resulting in complete recovery satisfy the criteria of the Guillain-Barré syndrome.[6] This patient developed hepatitis during a large military epidemic of the disease. The clinical course of the hepatitis differed in no respect from many other mild cases until the onset of neurological symptoms.

The occurrence of other virus diseases concurrently with infectious hepatitis has received comment. Hepatitis has been shown to be caused by a filterable agent. Symptoms indicating involvement of the central nervous system, as well as autopsy confirmation of the neural lesions, have been described. The occur-

rence of a myeloradiculitis may be of significance. Whether infectious neuronitis in this case was an intercurrent disease or there was present a specific association cannot be said. The situation, however, invites speculation as both infectious neuronitis and infectious hepatitis are thought to be virus diseases. It is of interest to note the previous occurrence of hepatitis in this patient, as a possible indication of a subnormal hepatic reserve at the start of his illness. If the occurrence of myeloradiculitis in a patient with hepatitis represents a complication of the latter, rather than an intercurrent infection, the patient herein described would be one most likely to suffer such a complication.

SUMMARY

A case of the Guillain-Barré syndrome in a patient convalescing from infectious hepatitis was presented. The possibility of the occurrence of the two diseases in the one patient representing a specific association rather than mere coincidence was discussed.

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ALLOXAN IN THE TREATMENT OF A CASE OF ISLET CELL CARCINOMA OF THE PANCREAS WITH LIVER METASTASES*

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ORGANIC hyperinsulinism has been recognized with increasing frequency in the last few years. It is most commonly due to adenomata of the islands of Langerhans. More and more case reports appear of successful surgical removal of these tumors with consequent alleviation of symptoms. At times there seems to be a general hypersecretion of insulin by the islet cells without discernible tumor in which resection of varying amounts of pancreatic tissue has been found effective. Carcinoma of islet cells occurs much less frequently. In these cases the tumor is often slow to grow and slow to metastasize. In a few instances

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metastatic islet cell carcinoma in the liver has been found in which the metastatic tumor cells apparently produce and release insulin. One of us [1] reported the fifth such case in the literature up to 1941. A few more have since been reported. All have died. Brunschwig [2] reported such a case which was treated with alloxan.

Since Dunn, Sheehan and McLetchie [3] described in 1943 a selective necrosis of the islands of Langerhans of the pancreas in rabbits produced by injection of alloxan, many articles have appeared on experimental studies of the effects of this chemical. Brunschwig [4] has discussed the action of alloxan and Joslin [5] has reviewed the literature up to April, 1944. Briefly alloxan, ureide of mesoxalic acid and a component of the uric acid molecule, causes selective necrosis of the islets of Langerhans in the pancreas and of the epithelium of the convoluted tubules in the kidneys in rabbits. Initial hyperglycemia occurs, followed by hypoglycemia in a few hours and later a hyperglycemia the duration of which largely depends on the size of the dose of alloxan. Houssay,[6] among others, has concluded from experiments on dogs that the liver is essential for the initial hyperglycemia. Dogs have been found more sensitive than rabbits to the drug. Goldner and Gomari [7] found that 100 mg. per kilogram body weight of alloxan given intravenously was fatal to dogs within eight hours. A dose of 75 to 100 mg. produced uremia with death in a week. A dose of 50 to 75 mg. produced typical diabetes without renal lesions. The animals were kept alive for several weeks. On histological examination many of the beta cells were found to have disappeared from the islets, profound vacuolization of the epithelium of the pancreatic ducts had occurred and fatty changes were found in the liver. Doses of 25 mg. were without effect.

Evidence is very meagre as to the effect of alloxan on the islet cells and convoluted tubules in man. Brunschwig [4] administered the chemical in proportionally much larger doses than had been used in animals to several patients with carcinoma. One of these patients had an insulin-producing islet cell carcinoma. This case was repeatedly but temporarily improved clinically by the drug. For short periods hypoglycemic attacks were much less severe and much less frequent and the patient gained weight. However, in no case, even when the dose had been increased to 1 gm. per kilogram body weight, was there later any evidence of significant damage to the islet cells or epithelial cells of the convoluted tubules on histological examination.

A patient with an insulin producing islet cell carcinoma with liver metastases came under our care in August, 1945. In spite of the none too encouraging reports in the literature it seemed worthwhile to administer alloxan to this patient because the prognosis was hopeless otherwise, and because temporary relief of symptoms might occur. It is desirable to place on record the results of the administration of alloxan to another human being.

Case Report

A 55 year old white female was admitted to the Memorial Hospital August 22, 1945. Her chief complaint was "going out like a light." For the previous six weeks she had had recurrent attacks of hypoglycemia for which her physician had prescribed four tablespoonsful of Karo corn syrup every four hours in addition to a general diet. The attacks were characterized by somnolence, hyperhidrosis, varying degrees of weakness, occasionally by maniacal tendencies and occasionally by unconsciousness requiring intravenous glucose.

Family history and past history were irrelevant except that in March, 1945 she was operated upon elsewhere because of vague abdominal symptoms and a normal appearing appendix was removed. No other pathologic condition had apparently been observed at operation.

Physical examination revealed a fairly obese woman weighing approximately 75 kilograms. She appeared apathetic, eyelids half closed, pupils equal, dilated but reacting to light and during accommodation. No significant abnormalities were evident on examination of ears, nose and pharynx. Examination of the chest revealed decreased breath sounds with dullness on percussion at the right base posteriorly. No râles were heard. The left lung was clear on percussion and auscultation. Examination of the heart revealed slight enlargement to the left and a soft blowing apical systolic murmur. The pulse rate was slightly increased. The blood pressure measured 140 mm. of Hg systolic and 60 diastolic. The abdomen was soft, obese and presented an old midline incisional scar and a recent appendectomy scar. The liver was palpable three to four fingers'-breadth below the right costal margin and was nodular especially in the epigastrium. There was tenderness above the umbilicus and beneath the liver on palpation. There also, incidentally, was a congenital abnormality of the right lower extremity with absent patella and fibula, foot drop, short achilles tendon and an irregular scar over the right thigh, a result of an operation on the right femur and hip joint 37 years previously.

The urine was yellow with a specific gravity of 1.015, alkaline in reaction and there was a very slight amount of albumin. The microscopic examination was normal. The urine was not significantly different on examination throughout the patient's course in the hospital except that on one or two occasions there were from 3 to 10 red cells in the microscopic examination. Hematology report: Red blood cells 3.6 million; white blood cells 12,600; hemoglobin 10.5 gm.; color index .91; mature neutrophiles 80 per cent; young neutrophiles 4 per cent; lymphocytes 15 per cent; and monocytes 1 per cent. Plasma sodium chloride 460 mg. per cent, serum amylase 55 per cent of normal; blood cholesterol 193 mg. per cent.

Course in Hospital: Hospitalization continued for 33 days during which time there occurred a total of 60 hyperinsulin reactions, varying in degrees from slight weakness, lethargy and perspiration to actual coma. For the first five days her average carbohydrate intake was approximately 180 gm. During this time she had 13 hypoglycemic reactions, five of which were severe. The blood sugar determination ranged from 49 to 62 mg. per cent. On the sixth and seventh days the carbohydrate intake averaged 550 gm.; and there were six hypoglycemic reactions, two of them severe during this two-day period.

On the ninth hospital day an exploratory laparotomy was performed. The operative notes were as follows:

The liver presented immediately upon opening, was considerably enlarged and studded over its surface both superiorly and inferiorly with discrete nodules grossly characteristic of carcinoma. These nodules were found in both right and left lobes, had a grayish yellow appearance and varied in diameter from a few mm. to 2.5 cm. Upon exposure of the pancreas, the head and most of the body were found to be of normal appearance and consistency, but upon approaching the tail portion a tumor mass, irregular over its surface, measuring roughly 4 by 6 cm. could be seen and felt. The gross appearance of this tumor was like that noted in the metastatic nodules in the liver. This portion of the pancreas was fixed posteriorly and seemed also adherent to the spleen and splenic flexure of the colon. An enlarged lymph node was present along the foramen of Winslow but it was not hard and apparently was not involved by the process in the pancreas.

The pathological report of the biopsy of the liver was consistent with carcinoma of island of Langerhans. The day following the exploratory laparotomy the patient

had a temperature of 104 degrees. Physical signs were those of respiratory embarrassment with a decrease in breath sounds at the right base posteriorly. No râles were heard. On roentgenographic examination there was evidence of fluid in the right lower chest cavity. No atelectatic areas could be found. Penicillin was administered in dosage of 120,000 units a day for five days. On the fifth day the temperature reached normal. During this febrile period the patient had no hypoglycemic symptoms. The average carbohydrate intake from the third to the seventh postoperative day inclusive was about 100 gm. per 24 hour period. The blood sugar level on the third postoperative day was 147 mg. per cent, on the fourth 163 mg. per cent and on the seventh 60 mg. per cent. It was on the seventh day that the temperature reached normal. Thereafter increasing amounts of carbohydrate were needed. From the tenth to the thirteenth postoperative day there were 11 moderately severe hypoglycemic reactions in spite of an average daily intake of 500 gm. of carbohydrate. Seven blood sugar determinations during this period ranged from 73 to 42 mg. per cent.

On the eleventh postoperative day 5 gm. of alloxan in a 1 per cent dilution in normal saline were given intravenously taking 65 minutes for the injections. There was moderate pain and slight swelling at the site of the injection of about 12 hours' duration. No systemic reaction was apparent. No local or general reactions were noted in any later injections. Beginning three days later, on the fourteenth postoperative day, 7.5 gm. of alloxan were given slowly intravenously in a 1 per cent solution daily for four days. The next two days, the nineteenth and twentieth postoperative days, 10 gm. of alloxan were given daily as a 2 per cent solution in normal saline containing 10 per cent glucose, taking 75 and 55 minutes respectively for the injections. On the twenty-first and twenty-second postoperative days 15 gm. of alloxan were given daily as a 3 per cent solution in normal saline containing 10 per cent glucose, employing 150 and 55 minutes respectively for the injections. In other words after a trial dose of 5 gm. on the eleventh postoperative day a total of 87.25 gm. of alloxan or 1.16 gm. per kilogram of body weight were given, divided in daily doses for nine consecutive days.

Before alloxan was administered the patient had no desire for food and it was necessary to increase the amount of parenteral carbohydrate. During the nine days of alloxan therapy, the average intake of carbohydrate was about 500 gm., the supplemental carbohydrate being given partly by gavage and partly by vein. There was no appreciable clinical effect of the alloxan. Blood sugar levels varied from 37 to 165 mg. per cent without any apparent relation to carbohydrate intake or administration of alloxan. The patient's general clinical course was downward. The last day that alloxan was given 800 gm. of carbohydrate seemed to be necessary to keep her out of coma. The blood sugar readings were 45 and 41 mg. per cent. Twelve hours after this latter blood sugar determination, without additional alloxan, she seemed slightly improved and the blood sugar was 228 mg. per cent and again 12 hours later still 293 mg. per cent with an intake of 475 mg. of carbohydrate in 24 hours. The patient took fluids well during the next 12 hours then suddenly went into coma and died. Five minutes after death the blood sugar was 45 mg. per cent.

Pathological Findings: Liver biopsy before alloxan treatment: The specimen (figure 1) contained carcinomatous tissue the cells of which were of medium size and tended to be somewhat elongated. The cytoplasm was abundant and stained slightly red with hematoxylin and eosin. The nuclei were central, somewhat elongated, and were rich in granular chromatin. The nuclei showed a moderate degree of variation in size and shape and mitotic figures occurred frequently. The tumor cells were arranged in masses with a tendency to form rows and imperfect glands. In a few small areas, masses of tumor cells, isolated in a rather abundant connective tissue stroma, had a general resemblance to islands of Langerhans, but

the resemblance was rather superficial and special stains showed no definite alpha or beta granules. In general, the carcinomatous tissue showed much greater resemblance to pancreatic duct than to islet cell tissue.

Autopsy (Performed 3½ hours post mortem): The body was well developed, diffusely jaundiced, and showed evidence of recent loss of weight. Heart and lungs

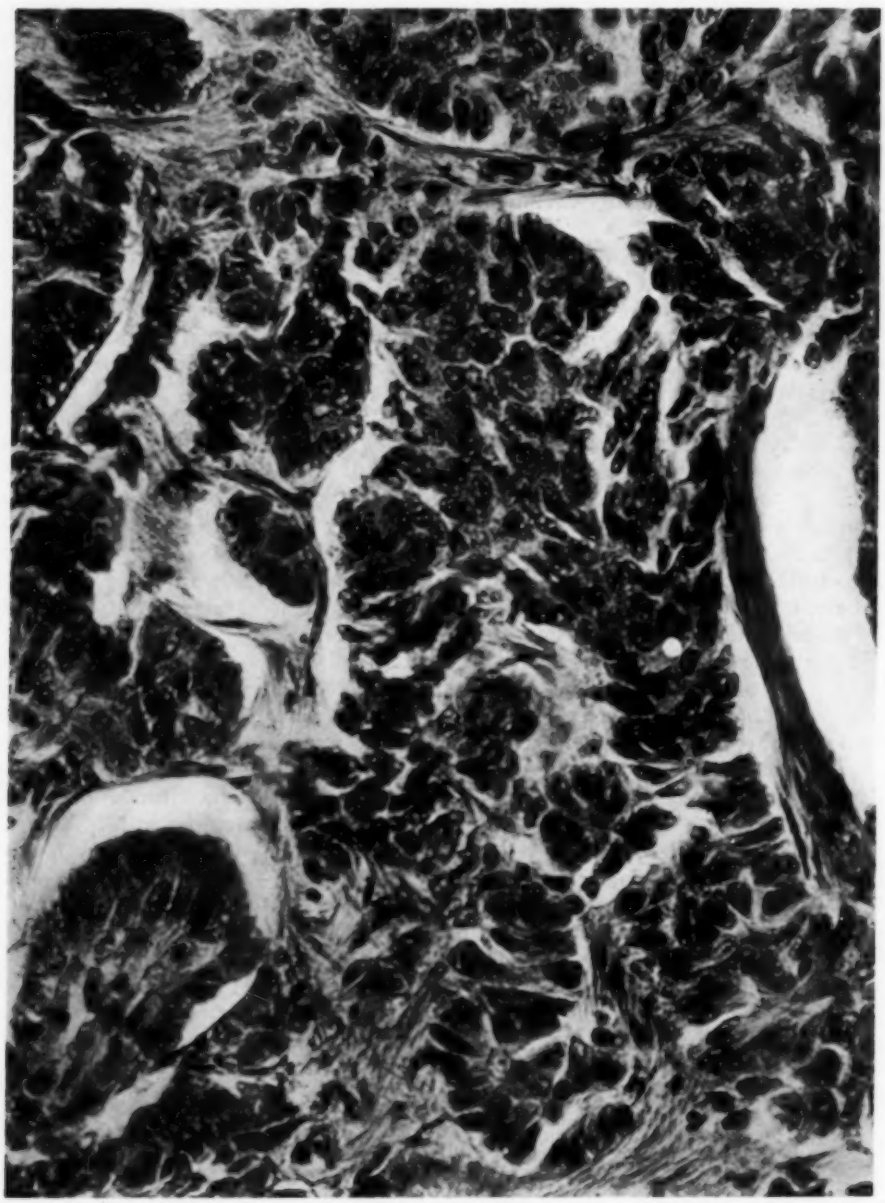

FIG. 1. Section from liver metastasis of pancreatic islet cell carcinoma. Before alloxan therapy. (× 345.)

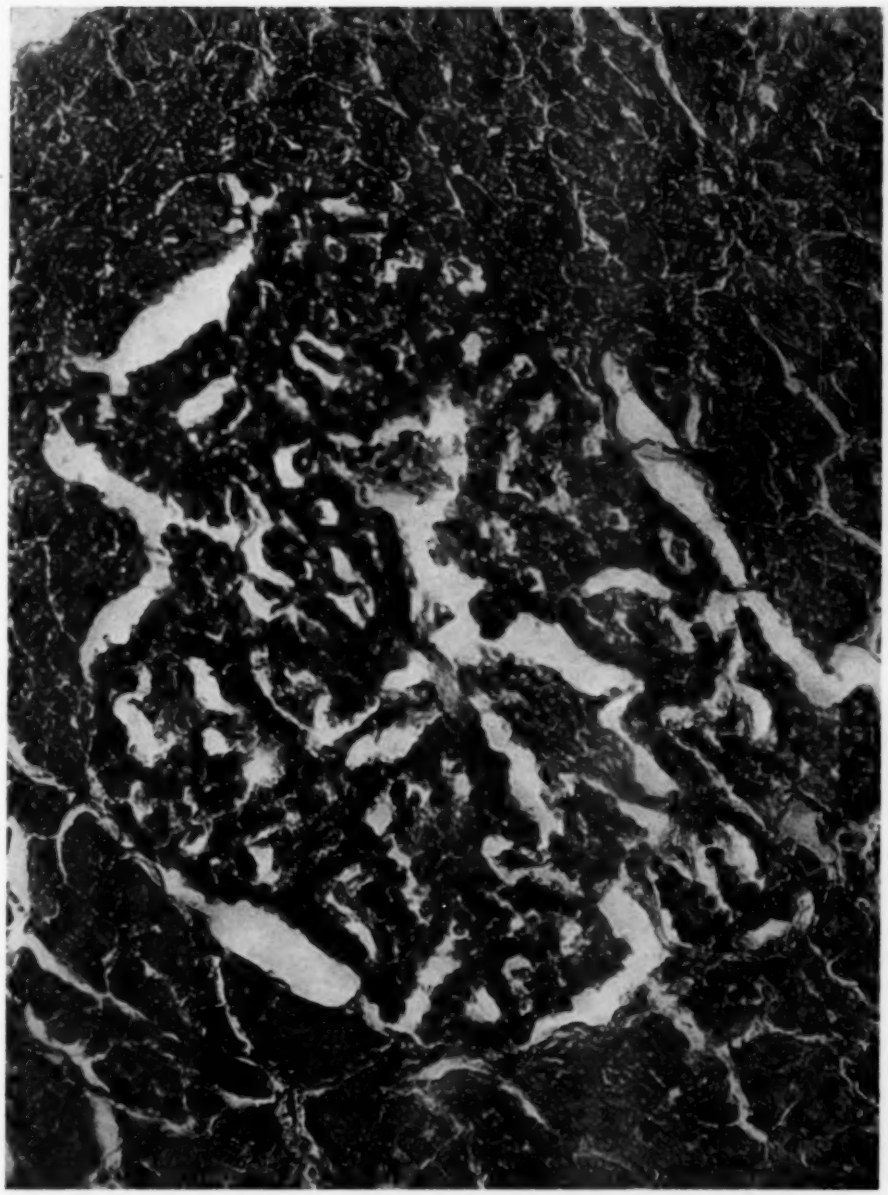

FIG. 2. Island of Langerhans after alloxan treatment, showing shrinkage. (× 345.)

were essentially normal. Numerous fibrous peritoneal adhesions were present beneath the laparotomy scars and around the tail of the pancreas. The spleen was essentially normal. The pancreas weighed 150 grams. The distal half of the organ, including the tail and about one half of the body, was involved in a mass of firm gray tumor tissue which cut with resistance and had the general appearance of a scirrhous carcinoma. Scar tissue adjacent to the tumor extended to the spleen and cardiac

portion of the stomach. The proximal half of the pancreas and the pancreatic duct were grossly normal. The portion of the organ not involved in cancer showed very little microscopic abnormality. The cells making up the islands of Langerhans were slightly atrophied, leaving small empty spaces between the islands and their capsules (figure 2). As far as could be made out by special stains, most of the cells were beta type and extremely few were alpha type. The acinar tissue appeared entirely normal. The tumor portion of the pancreas consisted of a markedly scirrhous carcinoma made up of polyhedral cells with a slight tendency to be columnar and to form duct-like structures. This appearance was quite different from that of the tumor in the metastatic sites where there was much less connective tissue and freer growth of the tumor cells. In the pancreas, the tumor cells were of medium size and contained a moderate amount of red-staining cytoplasm. Special staining showed no differentiation into alpha and beta cells. The nuclei were centrally located, medium sized, and showed a moderate degree of variation in size and shape with occasional mitotic figures. Most of the tumor cells were arranged in rather solid masses with a slight tendency to duct formation. The stroma consisted of dense connective tissue which occasionally contained small groups of tumor cells showing a rather striking resemblance to the islands of Langerhans. These cells showed the same shrinkage as in the tumor-free portion of the pancreas. Some portions of the tumor were necrotic and infiltrated with polymorphonuclear leukocytes.

The gastric mucosa was thin, slightly congested, and atrophied. Several fibrous adhesions roughened the peritoneal surfaces of the gastrointestinal tract and the appendix was absent.

The kidneys were markedly edematous and about twice normal size. On microscopic examination the epithelium lining the convoluted tubules was granular and in many places had lost cellular and nuclear detail.

Adrenals, breasts, thyroid, parathyroid, and pituitary glands were grossly and microscopically normal.

The brain was normal.

The lymph nodes in the vicinity of the gall-bladder neck and pyloric end of the stomach and in the retroperitoneal lumbar region were enlarged up to 2 cm. in diameter. They contained carcinomatous metastases similar in appearance to the primary growth and having a rather striking resemblance to pancreatic islands.

The liver weighed 4,350 gm. and consisted quite largely of tumor. Almost the entire right lobe was replaced by firm, slightly jaundiced gray tissue which cut with resistance and had the form of nodules varying from minute size up to large conglomerate masses. The remaining liver tissue showed no evidence of cirrhosis and the gall-bladder was normal.

The microscopic findings in the liver metastases at autopsy were compared with those in the carcinomatous liver tissue obtained by biopsy. Microscopically the tumor cells in the liver (figure 3) were considerably shrunken with the cytoplasm appearing more dense and staining a darker red than in the biopsy specimen (figure 1). The nuclei were also shrunken and appeared as relatively solid masses of chromatin. The degree of variation in the nuclei was about the same as in the biopsy specimen and there was no indication that the tumor was growing any more slowly. Elsewhere, the tumor cells were necrotic and the tissue was infiltrated with polymorphonuclear leukocytes.

Comment

The cause of the hyperglycemia which occurred 24 hours before death is uncertain. In the light of animal experiments referred to above one is tempted to speculate that possibly in this patient the dose of alloxan effective on the islet

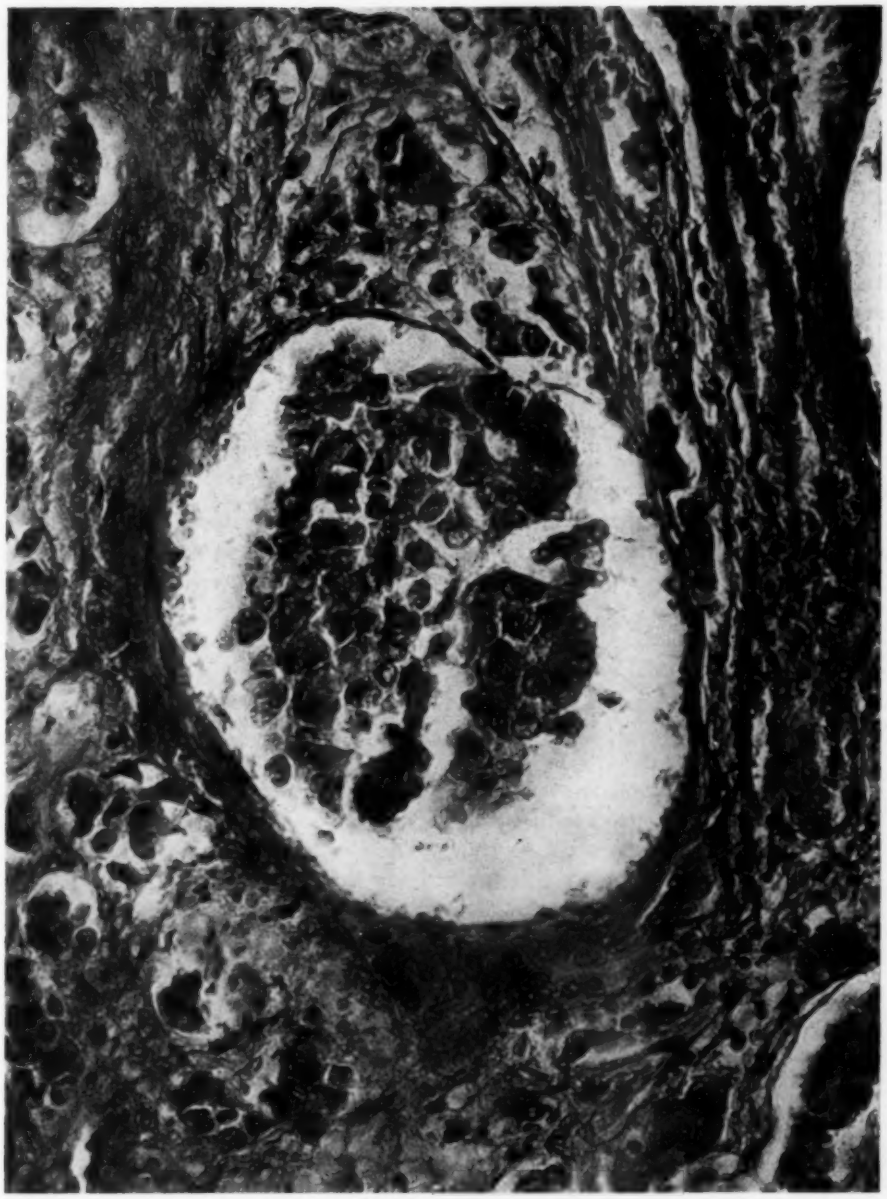

FIG. 3. Liver metastasis of pancreatic islet cell carcinoma: after alloxan therapy, showing shrinkage. (× 345.)

cells was reached on this ninth day of treatment, the so-called initial hyperglycemia occurred followed by sudden death in the secondary hypoglycemia. Animals which survive this hypoglycemia phase go into a second and perhaps permanent hyperglycemia. Histological studies of the liver and pancreas in this patient seemed to show shrinkage of nuclei and cytoplasm in the islet cells not

invaded by the tumor and similar shrinkage of the metastatic tumor cells in the liver as compared with the biopsy obtained before alloxan was administered. No necrosis was present. This may indicate one of the earlier stages in the effect of alloxan as interpreted by animal experimentation according to several authors.[8, 9, 10] Five minutes after an injection of a diabetogenic dose of alloxan, slight but definite changes are discernible in the nuclei and the cytoplasm of the beta cells with a suggestion of some diminution of their specific granules. From 10 to 15 minutes after the injection there is a definite reduction of granules. These changes affect first the beta cells at the centers of the larger islets. Before the end of one hour there is some shrinkage of the affected cells which appear more closely packed and there is corresponding widening of the pericapillary spaces. In this respect the findings in this case report seem similar. By the end of one to two hours in the experimental animal definite pyknosis of nuclei is evident and at the end of three hours there is cellular separation with homogeneous eosinophilic cytoplasm. Pyknotic nuclei with an increasing amount of karyolysis and evidence of complete disintegration and disappearance of individual cells is present from five hours onward.

It was unfortunate that we were unable to determine a blood level of alloxan. Leech and Bailey [8] have described a method for making such determinations. In the future alloxan blood levels may be helpful in arriving at optimum dosage. It is probable that in man the effective dose of the drug will be found much higher than that heretofore used. Further knowledge of the pathological and physiological effects of alloxan should soon be forthcoming from the many studies now being conducted.

Summary

1. A case of an insulin producing islet cell carcinoma of the pancreas with liver metastases is reported with autopsy findings.

2. The patient was given alloxan intravenously for nine consecutive days with a total dosage of 1.16 gm. per kilogram of body weight.

3. No clinical effect was observed attributable to the alloxan.

4. Histological examination at autopsy revealed slight evidence of tumor cell damage in the liver metastases as compared with biopsy findings taken before alloxan therapy was begun. Some shrinking of islet cells not involved in the tumor was found. The changes noted, however, were not nearly so marked as those reported in laboratory animals and their significance therefore is not clear.

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ACUTE FATAL POISONING FOLLOWING INGESTION OF A SOLUTION OF DDT*

By Irving M. Reingold, M.D., and Irving I. Lasky, M.D.,
Los Angeles, California

Solutions of DDT are now being widely used in the household as insecticides, and as such are definite hazards in accidental and suicidal poisoning. The amount of DDT in such solutions is of low concentration and toxicity; greater concern, however, should be given the solvents of the solutions. Neal and coworkers [1, 2, 3] of the National Institute of Health directed attention to the potential dangers of the solvents used in the DDT mixtures. In their reports, they showed that the ill effects in humans from the use of DDT mixtures were due to agents other than DDT in the mixtures. Recently we performed an autopsy upon a patient who swallowed approximately 150 c.c. of a solution of DDT with suicidal intent. We regard this death as a fatal poisoning due to kerosene, the solvent used in the solution, and wish to emphasize the hazards in the use of these preparations.

Case Report

History: The patient, a 23 year old negress, apparently in good health, and without known reason, swallowed approximately 150 c.c. of a commercial preparation of DDT. Almost immediately after the ingestion of the solution, she began vomiting; she complained of severe epigastric pain and vomited repeatedly. When she was seen by a physician, within two hours after the ingestion of the solution, she was comatose, and completely flaccid; her respirations were slow and labored, pulse slow and feeble, and pupils equally dilated. Gastric lavage produced a thick, yellow, oily, aromatic fluid which smelled like kerosene. The patient did not respond to therapy, and died within three hours after the ingestion of the solution.

Autopsy: The body was that of a well developed and well nourished young adult negress of the stated age of about 23 years, who weighed approximately 57 kilograms. There were no marks of external violence. The essential macroscopic pathology was found in the lungs and gastrointestinal tract. The lungs, on cut sections, disclosed

* Received for publication March 11, 1946.
From the Department of Pathology of the School of Medicine, University of Southern California, and the Coroner's Office of the County of Los Angeles.

edema, and irregular, dark red, firm areas of discoloration, measuring up to 3 to 4 cm. in greatest dimensions. These areas, which appeared to be recent hemorrhages, were present throughout the lungs but were more frequent in the lower lobes. The tracheo-bronchial passages were smooth and glistening. The stomach was slightly dilated and contained an oily aromatic fluid which resembled kerosene. There were several hemorrhages within the mucosa of the stomach which measured up to 2 to 3 cm. in greatest dimensions. The upper small intestine, which was markedly hyperemic, contained a large amount of the oily fluid similar to that found in the stomach. The liver and kidneys were markedly hyperemic but showed no other abnormalities. The remainder of the organs revealed no gross abnormalities. The brain and spinal cord were not examined.

The essential microscopic lesions were found in the lungs and stomach. Sections of the lungs disclosed large areas of recent hemorrhages; masses of extravasated red blood corpuscles were seen in alveoli, septums and bronchioles. These alternated with areas of edema and aerated alveoli. Sections of the stomach disclosed moderate edema of the mucosa and focal areas of recent hemorrhages. There was marked passive hyperemia of the abdominal viscera. The liver and kidneys revealed moderate cloudy swelling.

Discussion

The solution ingested contained 4 per cent of DDT, 4 per cent of "lethane," and 92 per cent of refined petroleum oil (kerosene). From the lesions observed at autopsy, and from the formula of the solution, kerosene, and not DDT, was considered to be the etiological agent of the fatal poisoning.

According to Deichmann, Kitzmiller, Witherup, and Johansmann,[4] in fatal cases of kerosene poisoning, death usually occurs in two to 20 hours. The fatal outcome is the result of the absorption of the kerosene from the gastrointestinal tract and its passage by way of the blood stream to the organs and tissues of the body, notably the lungs. The kerosene may be aspirated into the tracheo-bronchial tree. It is capable of producing severe corrosive lesions accompanied by local exudative inflammatory changes. Following the absorption there is evidence of generalized toxemia and depressant effects on the central nervous system. The most important changes, however, occur in the lungs, which disclose vascular and parenchymatous damage.

The chief histopathological findings in animals exposed to high concentrations of DDT, according to the investigators of the National Institute of Health,[5, 6] are moderate degenerative changes of the liver. In no organs are sufficient pathological changes found to account for the death of the animals. When given in sufficiently large doses, and usually over a long period of time, DDT may cause definite signs of poisoning, always preceded by indications of injury to the liver and kidneys.

It is unlikely that "lethane," the trade name for the aliphatic thiocyanate used in the preparation as a supplementary insecticide, was of any significance in causing the fatal poisoning. The oral lethal dose of "lethane" ranges from 0.05 c.c. to 0.14 c.c. per 100 grams of body weight—in dogs and rats, respectively.[7]

The sudden death (within three hours) and pathological findings in this case indicate acute poisoning due to the kerosene. The large areas of pulmonary hemorrhages and edema are seen in kerosene poisoning. Besides, there were no areas of necrosis or fatty degeneration of the liver or kidneys as are described in experimental poisoning with DDT. In addition, it is probable that the amount

of DDT in the ingested solution was not sufficient to cause fatal poisoning. The acute toxicity of DDT given orally to the experimental animal is not of a high order. For instance, the oral median lethal dose for white rats ranges from 200 to 300 mg. per kilogram of body weight, for rabbits about 500, for dogs about 200, and for mice about 400.[8]

Apparently the pulmonary changes were brought about by absorption of the kerosene from the gastrointestinal tract and its subsequent excretion into the lungs, and not by the aspiration of the kerosene into the respiratory tract.[9]

The danger of poisoning from kerosene and other petroleum oil solvents used in solutions of DDT could be eliminated by using water-suspensions of DDT. Furthermore, the apparently low toxicity of DDT in such mixtures would exclude it as a hazard in acute poisoning.

Conclusions

1. Acute fatal poisoning followed the ingestion of a solution of DDT. The poisoning is considered to be due to kerosene, the solvent used in the solution.

2. The essential pathological findings were severe pulmonary hemorrhages and edema, gastric hemorrhages, and the presence of kerosene in the upper gastrointestinal tract.

3. The wide use of kerosene solutions of DDT as insecticides make them potential dangers in accidental and suicidal poisoning.

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EDITORIAL

PREFRONTAL LOBOTOMY FOR THE RELIEF OF UNBEARABLE PAIN

RELIEF of pain has ever been one of the cardinal functions of the physician. To this end possibly more time and energy have been devoted than to any of the other variegated healing practices, with the result that great strides have been taken toward perfecting anesthesia and analgesia as well as mechanical and surgical procedures for alleviating pain. Among the neurosurgical procedures that have been employed in the past may be listed alcohol injection of peripheral nerves, nerve section, sympathectomy, vagotomy, and chordotomy with division of the pain tracts in the spinal cord. Nevertheless, certain instances of intractable pain have defied all efforts of surgeons, physicians, and drug chemists to furnish complete and lasting relief. The miserable victims of such unbearable pain almost inevitably end up as drug addicts or suicides. It was in an attempt to fill the breach in our therapeutic armamentarium created by this group of unfortunate individuals that Watts and Freeman [1] resorted to a more radical, yet more subtle neurosurgical approach to the problem, namely psychosurgery in the form of prefrontal lobotomy.

Psychosurgery of this type was originally introduced as a method of treating certain grave psychotic states. Stimulated by the results of surgical treatment of mental disorders initiated by Moniz over a decade ago, Freeman and Watts [2] began to perform prefrontal lobotomies on patients with various types of psychoses. Early in their work they were impressed with the subtle change that took place in patients thus operated upon. These patients continued to manifest their same hallucinations and delusions, but were no longer bothered by them. Anxiety and fear were relieved, panic states no longer occurred, and obsessive thinking disappeared. It was the emotional reaction to the ideas that had disappeared. When this fact was more fully investigated, it was realized that the incisions in the frontal lobes interrupted the anterior thalamic radiation. Freeman and Watts believe that the frontal lobes subserve the functions of foresight and insight, particularly as related to the self, and that it is in relation to these ego functions that the affective coloring supplied by the thalamus is of overwhelming importance for the adjustment of the individual in his social milieu.

The operative mortality was only 3 per cent, but, although the results of prefrontal lobotomy were highly gratifying in a reasonably large percentage of the 260 psychotic patients followed from six months to nine years after operation, the authors frankly admit that the patients were far from

[1] WATTS, J. W., and FREEMAN, W.: Psychosurgery for the relief of unbearable pain, Jr. Internat. Coll. Surg., 1946, ix, 679.

[2] FREEMAN, W., and WATTS, J. W.: Prefrontal lobotomy: survey of 331 cases, Am. Jr. Med. Sci., 1946, ccxi, 1.

healthy, particularly at first. In undergoing this operation they had exchanged one form of abnormal behavior for another. Whereas during the psychosis they had been too preoccupied with themselves, following operation they were at the mercy of every passing external stimulus. The emotional intensity characteristic of the psychosis gave way to the emotional shallowness of the postoperative state, and the imaginative activity which had been at its height during the psychosis underwent more or less permanent reduction.

Patients who made a satisfactory recovery were, however, far from inanimate clods. They were for the most part cheerful, friendly, uncomplaining, outspoken, and buoyant. They fell in with the mood of their companions, were quick to follow suggestions and were not embarrassed, glum or self-conscious. They took an active interest in everything that went on about them, read the papers, attended movies, worked regularly and played games with intelligence and foresight. With them the emotional component of foresight and insight was sufficient for meeting external situations of moderate complexity. It seemed, however, that introversial preoccupation was no longer possible. If asked about themselves and their previous troubles, they might recall various ideas or particular episodes, but without concern, and many patients had a more or less complete amnesia for the whole psychotic period.

Among the 360 patients with nervous and mental disorders upon whom Watts and Freeman performed lobotomies were a number who complained of unbearable pain. Their complaints of pain appeared excessive and out of proportion to the painfulness of the condition itself. Following lobotomy, there was not only a disappearance of the anxiety, apprehension, and nervous tension, but the incessant complaints of pain were no longer heard. These observations led the authors to employ psychosurgery for relief of pain in selected cases of radiculitis, carcinoma, and tabes dorsalis. The individuals were known to be in great pain and yet the fear of pain seemed to be an equally important factor. In this group of patients the complaints about pain also ceased after prefrontal lobotomy and it was possible to reduce or discontinue entirely the use of narcotics. Although the complaining ceased and the patients no longer requested hypodermics and appeared comfortable and in good spirits, when asked directly about pain, some admitted it was still present. In fact, they stated that the pain was exactly as it was before the lobotomy. Apparently psychosurgery alters the individual's reaction to pain without materially changing his ability to feel pain. Perception of pain is still present, but the psychological reaction to pain is changed. Pain may be present, but when it no longer raises a mental picture of future disability or death and what this may mean to one's family, it can then be borne with equanimity.

This entire concept of affording relief from unbearable pain by altering the victim's reaction to pain is indeed a fascinating one. To be sure, pre-

frontal lobotomy is a drastic and radical procedure, to which we should resort only in carefully selected instances after more conservative measures have failed to afford relief. However, it may prove to have a very real place in the therapy of severe tabetic crises, metastatic malignancy, and other conditions characterized by excruciating pain, either persistent or paroxysmal.

W. H. B.

REVIEWS

A Primer of Electrocardiography. By GEORGE BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine; Senior Visiting Physician, Charity Hospital; Consultant in Cardiovascular Diseases, Ochsner Clinic; and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane University School of Medicine; Assistant Visiting Physician, Charity Hospital, New Orleans. 215 pages; 24 × 15 cm. 1946. Lea & Febiger, Philadelphia. Price, $3.50.

This small volume is intended for the beginner in electrocardiography. It is profusely illustrated by diagrams only. Controversial questions are avoided. The tone is rather didactic. Theory is adequately covered. It is recommended to the medical student and to the beginner in electrocardiography.

W. J. L.

Diseases of the Retina. By HERMAN ELWYN, M.D., Sr. Assistant Surgeon, New York Eye & Ear Infirmary. 587 pages; 23.5 × 16 cm. 1946. The Blakiston Company, Philadelphia. Price, $10.00.

The presentation of the material is systematic and thorough, the book being divided into eight parts under which all retinal diseases are classified. There is ample discussion of the diagnosis, pathology, and treatment of all the commoner diseases, and most of the rarer retinal conditions. The association of retinal vascular disease with systemic disease is adequately emphasized and this section should be of great value to ophthalmologists and internists alike.

The illustrations in this volume have been collected from many sources. They aptly illustrate many conditions. In a work of this character, however, one might have expected to find more original drawings or photographs from the author's clinical practice.

The clarity of expression and the systematic presentation of the subject more than offset any adverse comment. There is no doubt that such a modern text on the retina will fill a much needed vacancy in our ophthalmic literature.

F. E. K., JR.

Treponematosis. By ELLIS H. HUDSON, M.D., D.T.M. & H.; Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D. ScD., F.A.C.P., F.R.C.P. 122 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, $2.50.

In this analytical history of treponematosis the author furnishes a convincing explanation of the development of syphilis. His analysis of the debated relationship of the discovery of America by Columbus and the spread of syphilis in Europe is of great interest. The discussion of the autogenic and clinical relationship between yaws and syphilis is expertly handled. Classification, clinical features, pathology and epidemiology of diseases caused by the treponemas are presented in scholarly fashion.

T. E. W.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Recent Advances in Clinical Pathology. By various authors. Edited by S. C. DYKE, D. M. (Oxon), F.R.C.P. (London). 468 pages; 21 × 14 cm. 1947. The Blakiston Company, Philadelphia. Price, $5.50.

Experiences with Folic Acid. By TOM D. SPIES, M.D. 110 pages; 24 × 15.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, $3.75.

Clinical Pediatrics. Oxford Medical Outline Series. By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. 409 pages; 22 × 14.5 cm. 1947. Oxford University Press, New York. Price, $4.00.

Pharmacopoeia of the United States. Thirteenth Edition. By authority of the United States Pharmacopoeial Convention. 956 pages; 23.5 × 16 cm. 1947. Mack Publishing Company, Easton, Pa. Price, $8.00.

The Development of Inhalation Anaesthesia (with special reference to the years 1846–1900.) By BARBARA M. DUNCUM, Nuffield Department of Anesthetics, University of Oxford. 640 pages; 23 × 14.5 cm. 1947. Oxford University Press, New York. Price, $12.00.

Mental Mischief and Emotional Conflicts. Psychiatry and Psychology in Plain English. By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago. 396 pages; 24 × 16 cm. 1947. C. V. Mosby Company, St. Louis. Price, $6.00.

Maladies et Syndromes Rares Ou Peu Connus. Description Clinique-Repertoire des Signes et Liste des Noms Propres. By A. AIMES, Professeur à la Faculté de Médicine de Montpellier. 208 pages; 23 × 15.5 cm. 1946. Masson et Cie, Paris.

La Reticulose Histiomonocytaire. By P. CAZAL, Chef de Clinique à la Faculté de Médicine de Montpellier. 196 pages; 25.5 × 16.5 cm. 1946. Masson et Cie, Paris.

Education for Responsible Living. Third Printing. By WALLACE B. DONHAM, LL.D., L.H.D. 309 pages; 22 × 14.5 cm. 1946. Harvard University Press, Cambridge, Mass. Price, $3.00.

Dr. Samuel Guthrie, Discoverer of Chloroform. By JESSE RANDOLPH PAWLING, M.D., M.A., F.A.C.P. 123 pages; 22.5 × 14.5 cm. 1947. Brewster Press, Watertown, N. Y. Price, $3.50.

Allergy in Theory and Practice. By ROBERT A. COOKE, M.D., Sc.D., F.A.C.P., Director Dept. of Allergy, Roosevelt Hospital, N. Y. C. 572 pages; 24 × 16 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $8.00.

COLLEGE NEWS NOTES

Additional Life Members

The College is gratified to announce that, under date of May 7, 1947, the following Fellows became Life Members of the College:

Barnett Greenhouse, New Haven, Conn.
Standiford Helm, Evanston, Ill.

Registration Statistics

Twenty-eighth Annual Session

Chicago, April 28–May 2

The registration at the Twenty-eighth Annual Session was the largest that the College has ever had. The registration figures, tabulated according to categories of attendants, are given below. It is interesting to note that the number of persons attending was more than double that of the last Annual Session held in Chicago, which was in 1934. The extraordinary program of entertainment, which was prepared by the Ladies Committee, is believed to be responsible for the large increase of attendance by wives of registrants. The reason for the rather surprising drop in the number of students who attended the Morning Lectures and General Sessions has not been ascertained.

	Members	Guest Physicians	Guest Non-Physicians	Students	Exhibitors	Ladies	Total
Chicago (1947)	1694	1382	70	137	518	609	4410
Philadelphia (1946)	1539	1129	23	485	503	358	4037
St. Paul (1942)	827	541	43	75	200	162	1848
Chicago (1934)	690	660		420	194	121	2085

The Association of American Physicians
60th Annual Meeting

The 60th Annual Meeting of the Association of American Physicians was held at Atlantic City, New Jersey, during the first week of May, 1947. Dr. A. H. Gordon, of Montreal, was elected President, succeeding Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia; Dr. Francis G. Blake, F.A.C.P., New Haven, was elected Vice-President; Dr. Walter Bauer, F.A.C.P., Boston, Treasurer; Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Recorder; and Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Secretary. Dr. Joseph T. Wearn, F.A.C.P., Cleveland, heretofore Secretary, was elected a Councilor. Dr. Eugene F. Dubois, F.A.C.P., of Cornell University Medical School, New York City, was awarded the George M. Kober Medal for "marked contributions to medicine during his career."

General Kirk to Retire as Army Surgeon General

On the expiration, May 31, 1947, of the term of Major General Norman T. Kirk, F.A.C.P., as Surgeon General of the U. S. Army, he will be succeeded in that office by Brigadier General Raymond W. Bliss. Dr. Bliss graduated from the Tufts College

Medical School in 1910. He entered the Army shortly thereafter and has served with distinction through both World Wars. Dr. Bliss did postgraduate work at the Army Medical School and, in surgery, at the Harvard Medical School. Since January, 1946, he has held the position of Deputy Surgeon General.

Brigadier General George E. Armstrong has been nominated to succeed General Bliss as Deputy Surgeon General. Dr. Armstrong graduated from the University of Indiana Medical School and was commissioned in the Army in 1926. Since June of last year, he has been Chief of the Personnel Division of the Surgeon General's office.

General Practice in Hospitals

The following resolution, which was passed by the House of Delegates of the American Medical Association last December, is thought to be of sufficient interest to readers of the Annals of Internal Medicine to be reprinted here in full.

"Whereas, The House of Delegates of the American Medical Association has established an individual section on the general practice of medicine; and

"Whereas, The general practitioner has been recognized as a separate branch in the medical profession; and

"Whereas, This group has shown its interest in this section by registering 939 members in the section at the 1946 American Medical Association meeting in San Francisco; and

"Whereas, Their scientific section meetings were well attended; and

"Whereas, The House of Delegates has already voiced its approval of such sections in the separate state and county societies that are component parts of the American Medical Association; and

"Whereas, Sections on general practice have been started in some recognized hospitals that are approved by the American College of Surgeons and the Council on Medical Education and Hospitals and have been accepted by those bodies; and

"Whereas, Many hospitals have not established general practice sections in their visiting active staffs and their governing heads are doubtful whether such action has the approval of the bodies which set up the rules and regulations for the approval of their hospitals for interns and residents; therefore be it

"Resolved, That hospitals should be encouraged to establish general practitioner services. Appointment to a general practice section shall be made by the hospital authorities on the merits and training of the physician. Such a general practice section shall not per se prevent approval of a hospital for the training of interns and for residencies. The criterion of whether a physician may be a member of a hospital staff should not be dependent on certification by the various specialty boards or membership in special societies."

Colonel Robert H. Lowry, (MC) USA, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit for his distinguished services as Commanding Officer of the General Dispensary, and as Surgeon of the Military District of Washington, February, 1943, to August, 1946.

Commander Paul H. Morton, (MC), USN (Associate) Parris Island, S. C., has been awarded the Air Medal for his valuable activities in improving the physical and mental standards of our Naval aviators who were charged with protecting our supply lines in the English Channel during the last war.

Dr. Francis E. McDonough, F.A.C.P., Boston, Mass, is a recipient of the Legion of Merit. As a medical officer in the A.U.S., Dr. McDonough had the responsibility

of safeguarding the health of bomber command personnel in India and China. This award was made in recognition of the unusual success which he had in performing this duty.

Dr. Ward A. Darley, Jr., Denver, College Governor for Colorado, has been appointed Director of the University of Colorado Medical Center, which includes the University's Schools of Medicine and Nursing, as well as the Colorado General Hospital and the Colorado Psychopathic Hospital.

Dr. Leon Unger, F.A.C.P., Chicago, was installed as President at the recent meeting of the American College of Allergists. At this meeting Dr. Hal McCluney Davison, F.A.C.P., Atlanta, Ga., was elected to the position of President-Elect.

Dr. F. William Sunderman, F.A.C.P., Philadelphia, Pa., has been elected Vice President of the American Board of Pathology.

Dr. John W. Ferree, F.A.C.P., New York, N. Y., has been appointed Associate Executive Director of the National Health Council, New York. Dr. Ferree was formerly a division director of the American Social Hygiene Association. He is a graduate of the University of Indiana Medical School, and has been engaged in public health work since 1936.

Dr. Howard F. West, F.A.C.P., Los Angeles, President of the American Heart Association, has announced the appointment of Dr. Charles A. R. Connor (Associate), New York, as Associate Medical Director. Dr. Connor, a graduate of the New York University College of Medicine, is affiliated with the teaching staff of that school and also holds appointment as Assistant Chief of the Cardiovascular Clinic in the Lenox Hill Hospital and as Attending Consultant to the Veterans Administration. Dr. Connor will assist the Association's Medical Director in the task of stimulating research and the dissemination of information concerning diseases of the heart and circulation.

The College wishes to express its gratitude to Dr. J. R. Pawling, F.A.C.P., Watertown, N. Y., for his kindness in sending to the College Library of Publications by Members a copy of his book entitled, "Dr. Samuel Guthrie, Discoverer of Chloroform," published by the Brewster Press, Watertown, N. Y., 1947.

Dr. Franklin C. Cassidy, F.A.C.P., formerly Manager of the Veterans Administration Hospital, Outwood, Ky., has recently been assigned to the position of Manager at the Veterans Administration Hospital, located at 1025 Lamar Avenue, Memphis, Tenn. This hospital is in process of being converted from the care of general medical and surgical patients to an institution devoted exclusively to the care of the tuberculous.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to May 13, 1947, inclusive).

Charles L. Anderson, Jackson Heights, N. Y. (Lt. Col., MC, AUS)
Mackinnon Ellis, Bryn Mawr, Pa. (Comdr., MC, USNR)
Robert C. Manchester, Norfolk, Va. (Comdr., MC, USNR)
Joseph D. Landry, New Orleans, La. (Capt. MC, AUS)
Richard M. Nay, Rochester, Minn. (Major, MC, AUS)

OBITUARY

DR. MARK ATKINS BROWN

Mark Atkins Brown, M.D., F.A.C.P., was born in Cincinnati, Ohio, on October 19, 1874, and died January 13, 1947, at the Christian R. Holmes Hospital of cerebral hemorrhage.

Dr. Brown studied at the University of Cincinnati College of Medicine, receiving his M.D. degree in 1894. His long career as an outstanding internist and teacher in Cincinnati is marked by the following appointments: Professor of Materia Medica and Therapeutics, Cincinnati College of Medicine and Surgery, 1897–1898; Professor of Physical Diagnosis, Miami Medical College, 1898–1901; Attending Physician, Cincinnati General Hospital, 1901–1918; Assistant Director, 1918–1931; Professor of Medicine, University of Cincinnati College of Medicine and Surgery, 1901–1931.

Mark Brown was a member of the Academy of Medicine of Cincinnati and the Ohio State Medical Association; a Fellow of the American Medical Association, and, since 1931, of the American College of Physicians.

It is noteworthy that in the thirty years during which Dr. Brown was Professor of Medicine, the College of Medicine grew and developed as a University unit, in great part due to the influence of his high competence and unstinted devotion. It is characteristic of his great heart and his loyalty to the institution that, in his will, he named the University as beneficiary to receive, after the death of his widow, one-half of his estate, the income to be used for the benefit of the department in which he had served. Thus the good that Dr. Mark Brown did in his lifetime will continue perpetually.

M. A. BLANKENHORN, M.D., F.A.C.P.,
Governor for Ohio

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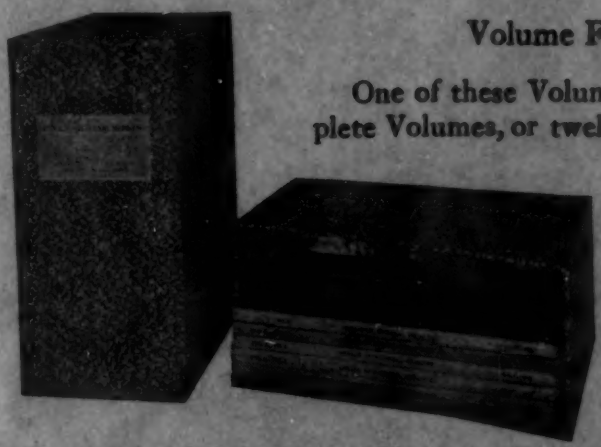

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